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Syntheses of azepinoindole alkaloids cimitrypazepine, fargesine and hyrtioreticulins C & D

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**Syntheses of azepinoindole alkaloids cimitrypazepine, fargesine and
hyrtioreticulins C & D**

Ganesh Ghimire

**Dissertation submitted
to the Eberly College of Arts and Sciences
at West Virginia University**

in partial fulfillment of the requirements for the degree of

**Doctor of Philosophy in
Chemistry**

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reaction, palladium-catalyzed**

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ABSTRACT

Syntheses of azepinoindole alkaloids cimitrypazepine, fargesine and
hyrtioreticulins C & D

Ganesh Ghimire

The Watanabe-Cenini-Söderberg reductive *N*-heterocyclization has emerged as a powerful tool for the synthesis of a variety of functionalized indoles. Söderberg's elaboration of this methodology has been utilized as a late-stage cyclization protocol for the synthesis of azepinoindole alkaloids, a class of natural products characterized by an azepane skeleton fused with an indole ring. Short syntheses of the naturally occurring azepino[5,4,3-*cd*]indole alkaloids, cimitrypazepine, fargesine, and the diastereomeric hyrtioreticulins C & D have been completed starting from commercially available tetra-substituted benzene derivatives. The key azepinoindole core in each case was assembled via an intramolecular Mizoroki-Heck reaction followed by a Watanabe-Cenini-Söderberg reductive *N*-heterocyclization. Synthesis of aurantioclavine using a similar strategy is currently underway.

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Chapter 1

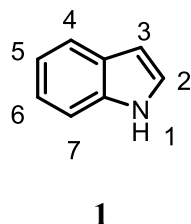
Introduction to Indole and Azepinoindole, Strategies Towards Azepinoindoles

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1.1 Introduction of Indole

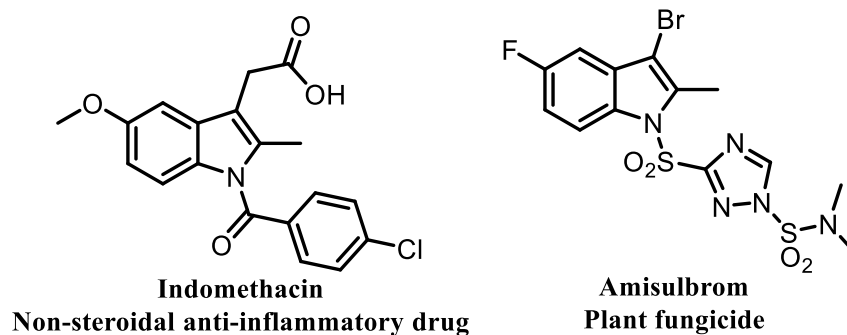
Indole (**1**), also called benzopyrrole, is an aromatic heterocyclic compound in which a pyrrole ring is fused to a benzene ring (Figure 1).

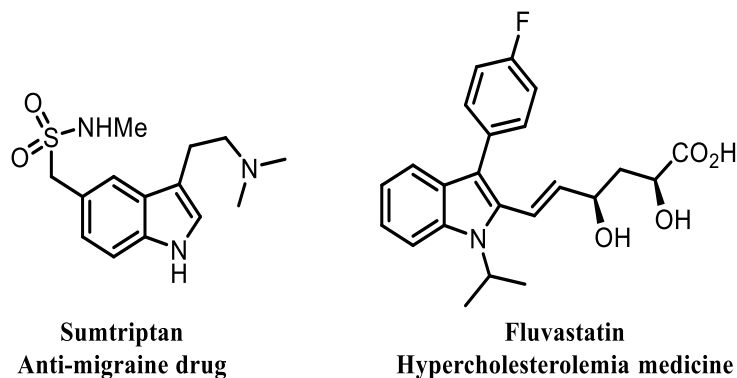
Figure 1: Structure and Numbering of Indole



After their discovery in 1860's by Baeyer and coworkers,¹ indole-based compounds are perhaps the most highly studied organic molecules due to their widespread application in industries, pharmaceuticals, agrochemicals, dyes, perfumes and dietary supplements (Figure 2).² Indoles are considered 'Privileged structures' in drug discovery as they are capable of binding to multiple receptors with high affinity.^{3,4}

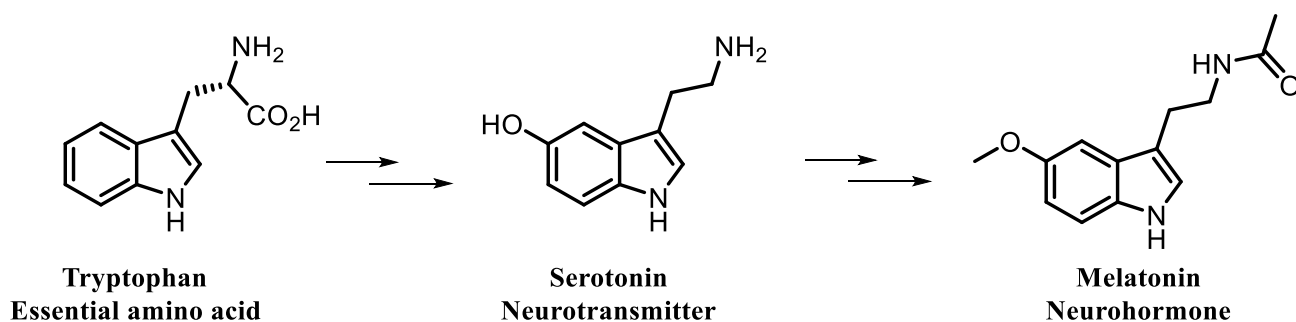
Figure 2: Indole Containing Drugs and Chemicals





The interest in indole chemistry was more intensified after 1930's when it was discovered that many natural products and bioactive molecules contain indoles as their core structures. The indole nucleus is embedded in many biological systems including the essential amino acid tryptophan, the neurotransmitter serotonin, and the mammalian hormone melatonin. Tryptophan is a structural constituent of many proteins as well as the biosynthetic precursor of serotonin, which in turn serves as the precursor of melatonin (Scheme 1). Serotonin plays a critical role in neuronal cell formation and maintenance, sleep, cognition, appetite, and mood, whereas melatonin is a natural bioregulator that induces and maintains sleep.^{5,6}

Scheme 1: Biosynthesis of Melatonin



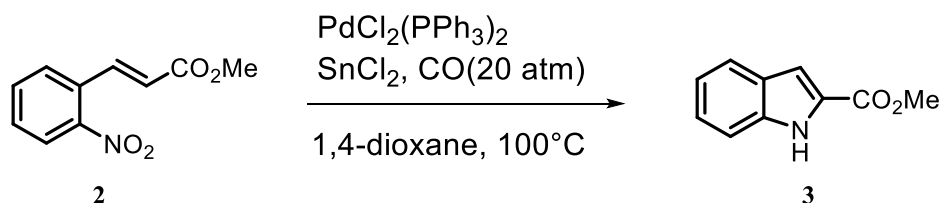
Tryptophan is also the biogenetic precursor of many indole alkaloids. Naturally occurring indole alkaloids are constantly getting more attention from the scientific community due to their intriguing structure and biological activity. Many endeavors are driven by structural complexity

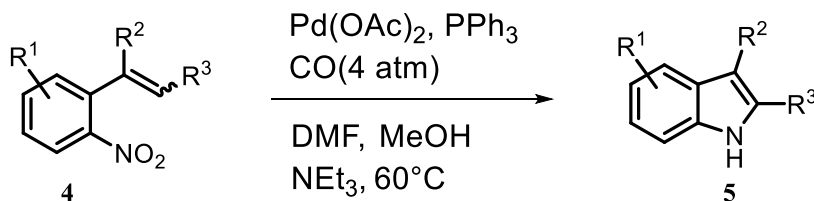
and their potential as drug candidates. Development of advanced isolation and characterization techniques has made their investigation convenient. As a result, many new indole alkaloids are reported annually. Synthetic attempts toward these complex indole structures may lead to reaction discovery and development. A number of methods have been reported as established routes for the preparation of indole and its analogs.⁷ Among the synthetic routes, there are quite a few transition metal- catalyzed or -mediated methods of indole synthesis.^{8,9,10} Among the plethora of methodologies used for indole synthesis, the Watanabe-Cenini- Söderberg reductive *N*-heterocyclization¹¹ has emerged as a powerful tool for indole synthesis, which will be discussed in the following section.

1.2 Watanabe-Cenini- Söderberg Reductive *N*-Heterocyclization

Although first discovered by Watanabe,¹² the reductive *N*-heterocyclization of *o*-nitrostyrenes to give indoles was extensively elaborated by Söderberg group establishing the methodology as a powerful synthetic method (Scheme 2). Although not unprecedented, the Söderberg method provides a number of significant improvements over previously reported conditions such as low temperature, mild reaction conditions and ease of work-up, because the only by-product formed is carbon dioxide.¹³

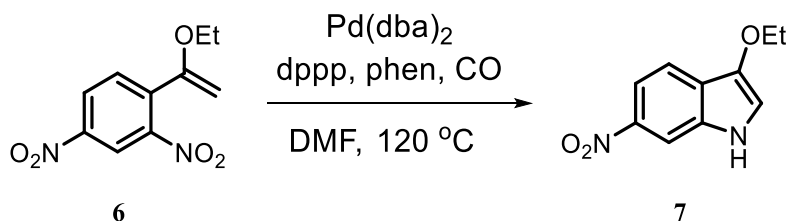
Scheme 2: Watanabe and Söderberg Reductive Heterocyclization





Sönderberg's method has been successfully applied to the synthesis of a number of indole analogs including tryptophan derivatives,¹⁴ bicyclic heteroaromatics,¹⁵ carbazole alkaloids,¹⁶ mushroom metabolites,¹⁷ and various natural products.¹⁸⁻²⁵ Through a detailed optimization study of the reaction conditions, it was observed that the $\text{Pd}(\text{dba})_2$ -dppp-1,10-phenanthroline system using DMF as solvent at 120°C under 6 atm of carbon monoxide (Scheme 3) was highly applicable to late stage indolization during many natural products syntheses.²²⁻²⁵

Scheme 3: Sönderberg Reductive *N*-Heterocyclization Optimized for Late Stage Indolization in Natural Products Synthesis

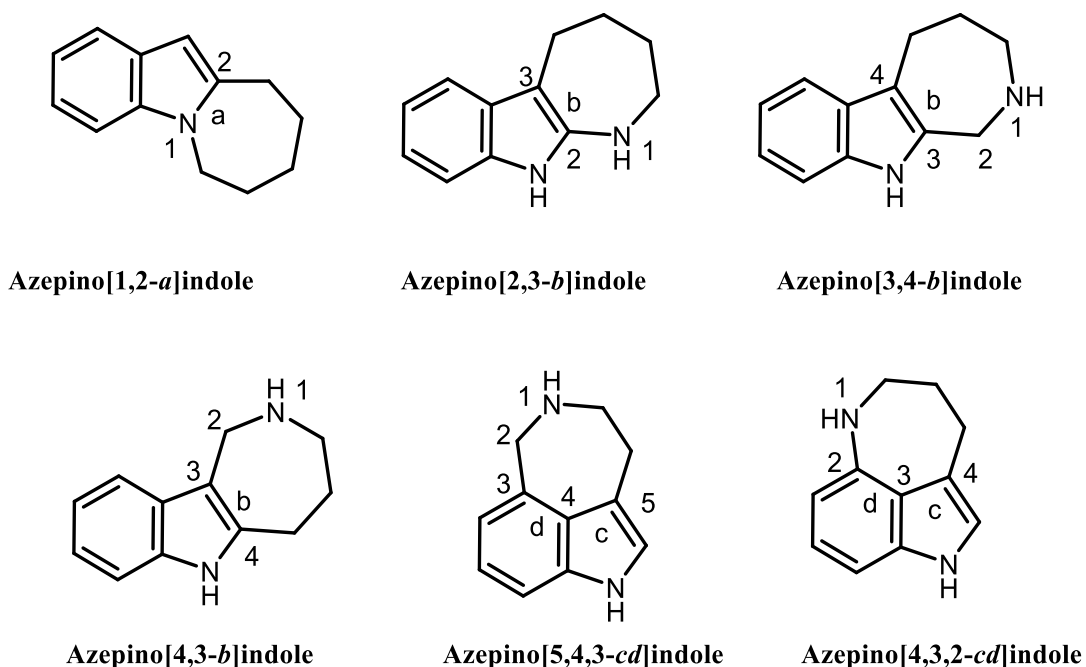


1.3 3,4-Fused Azepinoindoles

Azepinoindoles refer to the organic compounds in which a seven-membered ring containing nitrogen is fused with indole core. Azepinoindoles fused at 1,2-, 2,3- and 3,4- position of the pyrrole ring have been reported. Azepinoindoles are named according to the following scheme based on the fusion position of the azepine-ring with indole.²⁶ The nitrogen atom of the azepine ring is designated atom 1 and proceeds towards the pyrrole portion of the molecule

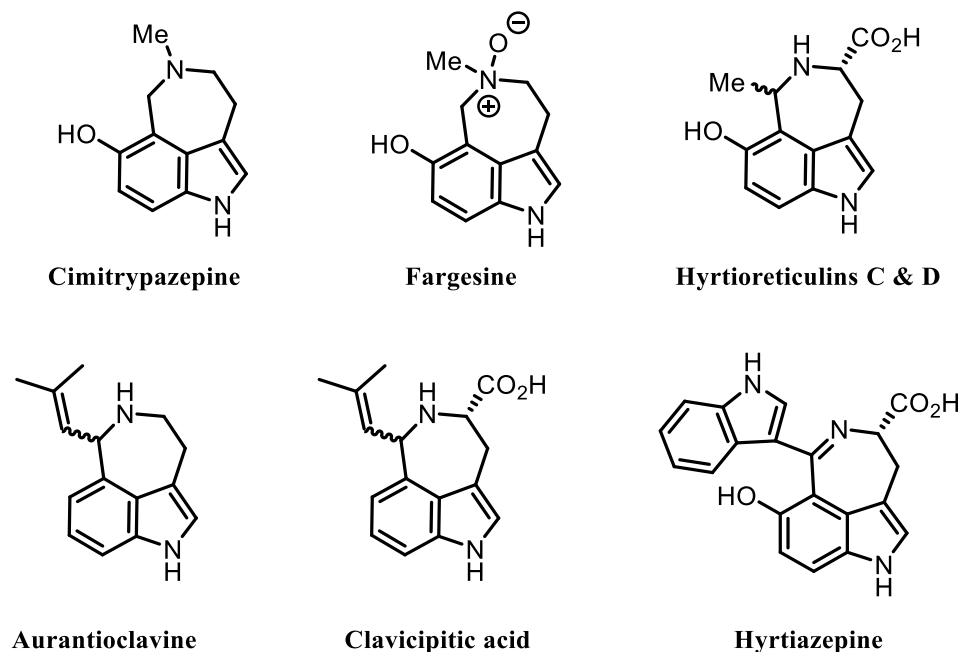
(Figure 3). The bonds in the pyrrole ring are named a, b, c and d to indicate where the azepine ring is fused. The numbering of fused atoms starts from the number of the atom closest to the pyrrole nitrogen.

Figure 3: Naming of Azepinoindoles



Naturally occurring azepino[5,4,3-*cd*]indoles have been isolated from diverse natural sources (Figure 4). This group of alkaloids include aurantioclavine isolated from the fungus *Penicillium aurantiovirens*,²⁷ clavicipitic acid from the fungus *Claviceps fusiformis*,²⁸ the diastereomeric alkaloids hyrtireticuline C and D from the marine sponge *Hyrtios reticulatus*,²⁹ fargesine from the roots and stems of *Evodia fargesii*,³⁰ cimitrypazepine from the roots and rhizomes of black cohosh, *Cimicifuga racemosa*,³¹ and bisindole alkaloid hyrtiazepine from *Hyrtios erectus*.³²

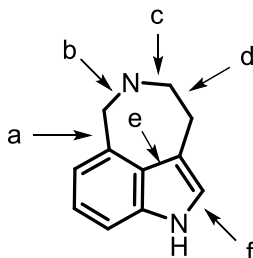
Figure 4: Naturally Occurring Azepino[5,4,3-*cd*]indoles.



1.4 Strategies Towards the Synthesis of Azepino[5,4,3-*cd*]indoles

Among the naturally occurring indoles, azepino[5,4,3-*cd*]indoles have been considered attractive synthetic targets because of their biological activities and intrinsic structural complexity. A variety of synthetic strategies have been used to prepare the azepino[5,4,3-*cd*]indole ring system and the most prevalent are functional group manipulations of 3,4-disubstituted indoles to form the azepine ring. The formation of the carbon-nitrogen bond **b** is the most commonly used approach in total synthesis^{33,34} although the formation of carbon-nitrogen bond **c**³⁵ and carbon-carbon bonds **a**^{36,37} and **d**³⁸ have been employed (Figure 5). The assembly of both the pyrrole and azepine rings onto a functionalized benzene ring is more unusual but sequential **f-e-b**,³⁹ **b** then **f**,⁴⁰ and **e** then **f**⁴¹ bond formations have been described. The latter methodologies offer perhaps more flexible routes to a variety of functionalized analogs compared to the use of a preassembled indole ring as the starting material.

Figure 5: Ring Disconnections Employed in Syntheses of Naturally Occurring Azepino[5,4,3-*cd*]indoles

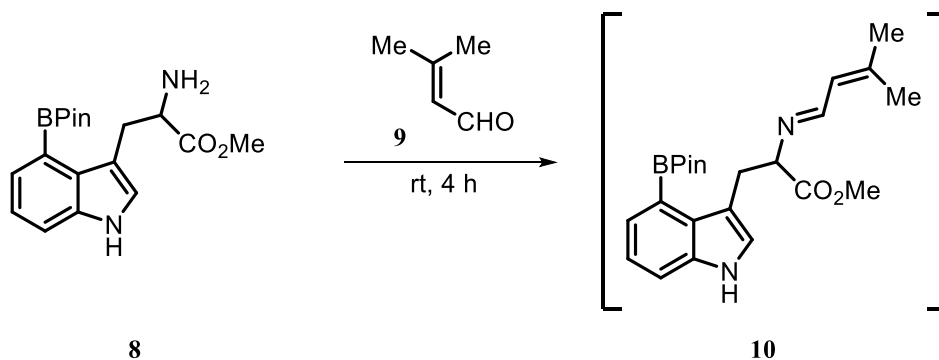


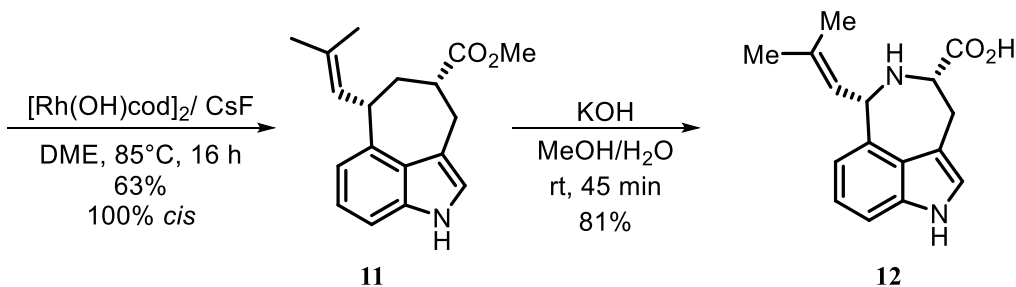
The ensuing sections will discuss various strategies used to synthesize 3,4-fused azepinoindoles.

1.4.1 Syntheses via ‘a’ Bond Formation

Cyclization at 4-position of indole via ‘a’ bond formation has been employed to complete the syntheses of various azepinoindoles. Bartoccini *et al.*⁴² used rhodium(I) catalyzed intramolecular imine hydroarylation of pinacolboranate ester **8** to synthesize clavicipitic acid **12** (Scheme 4). This one pot procedure allowed the regioselective introduction of the prenyl side chain at C-4 of tryptophan, forming a C–C bond at the least nucleophilic position (C-4) of the indole core, instead of at the highly nucleophilic positions C-2 and C-3.

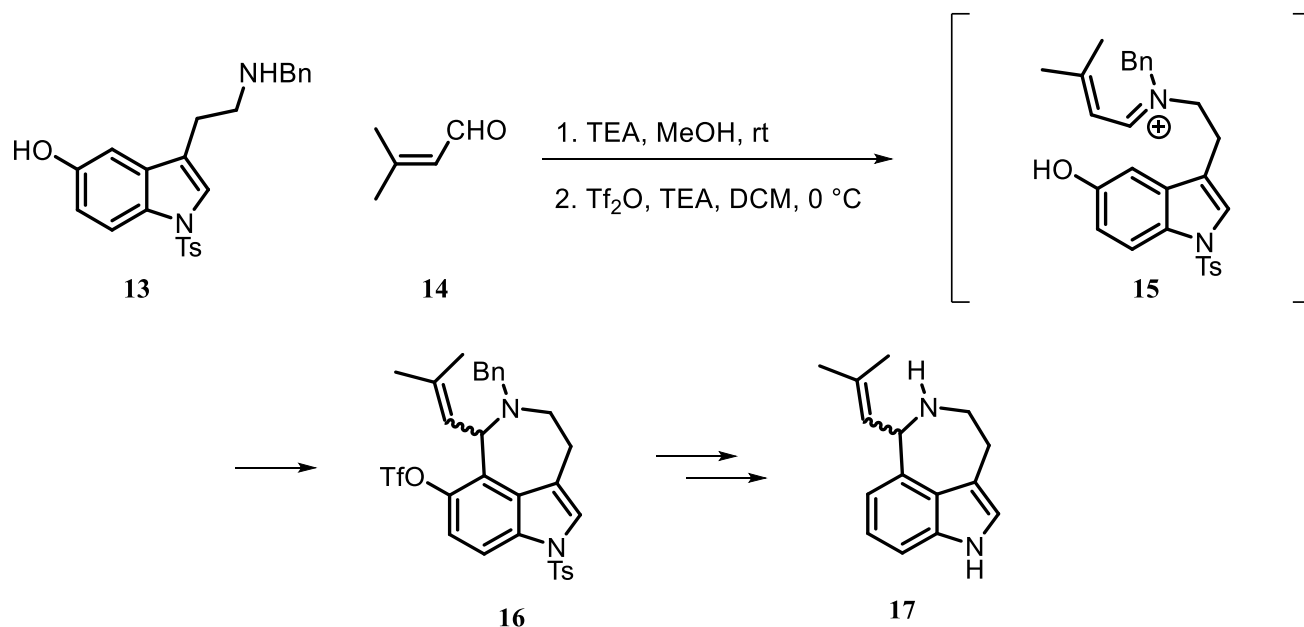
Scheme 4: Synthesis of Clavicipitic Acid by Bartoccini *et al.*





Use of base-promoted Pictet–Spengler reaction of in-situ formed iminium ion intermediate **15** to construct the azepine ring was pioneered by Yamada *et al.* The authors developed a one-pot procedure for the assembly of the azepino[5,4,3-*cd*]indole ring system through the reaction of *N*-benzylserotonin **13** (Scheme 5) or tryptophan with aldehydes and used this approach to provide a concise synthesis of aurantioclavine **17** and other *hyrtios* alkaloids.⁴³

Scheme 5: Syntheses Using Pictet-Spengler Reaction

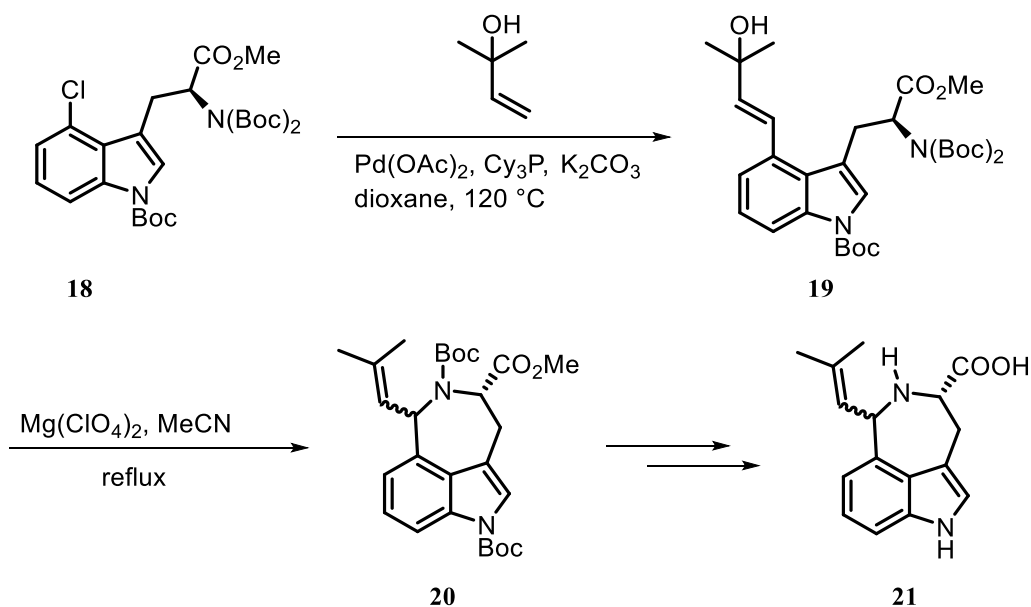


1.4.2 Syntheses via ‘b’ Bond Formation

In 2009, Xu *et al.*⁴⁴ obtained the azepinoindole via Lewis acid mediated S_N2' reaction. It was an accidental observation that they obtained cyclized product during removal of boc group

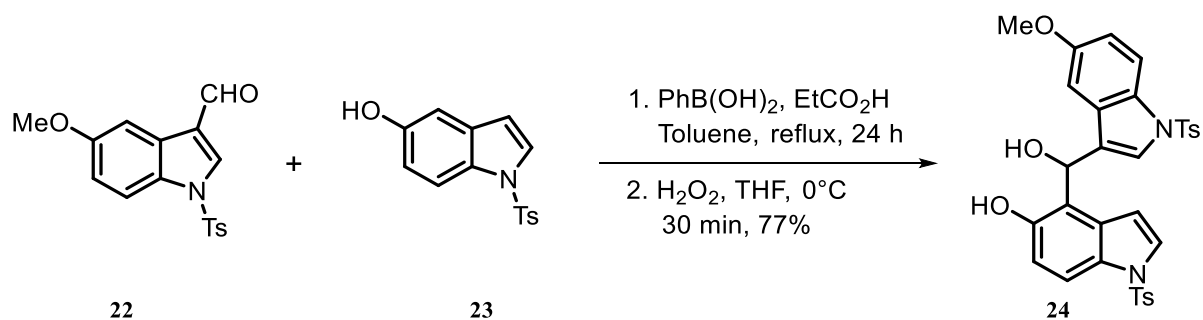
of **19** by magnesium perchlorate. Even though the exact mechanism has not been explored, it was postulated that Mg acting as Lewis acid activates the allylic -OH group and facilitates the S_N2' reaction to complete the synthesis of clavicipitic acid **21** (Scheme 6).

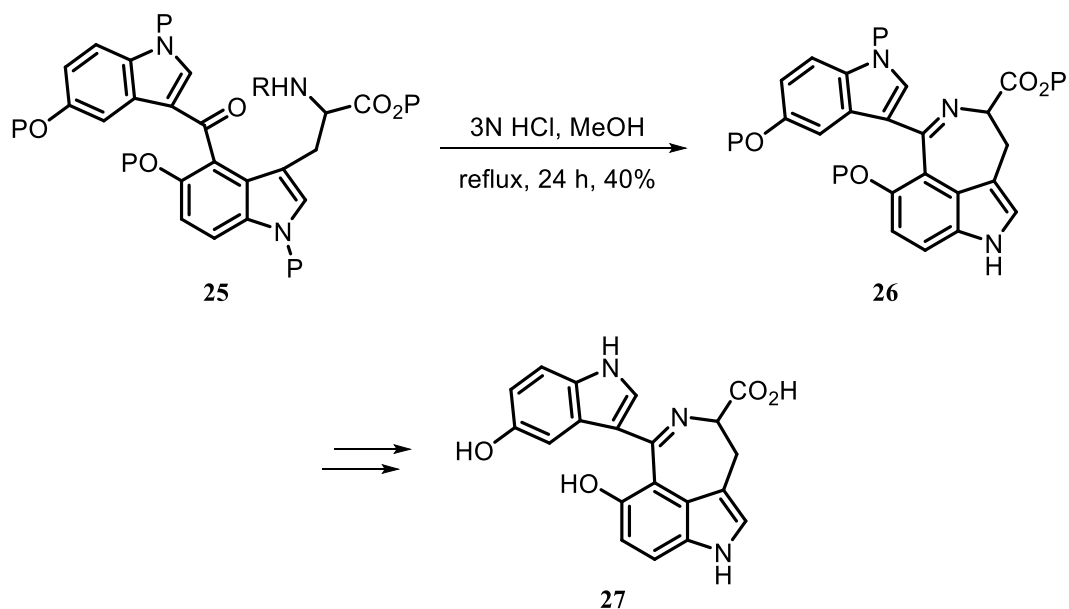
Scheme 6: Xu's Synthesis of Clavicipitic Acid



Ito *et al.*⁴⁵ used an ortho-selective α -hydroxyalkylation of indole **23** followed by intramolecular imination of resulting ketone **25** to assemble the azepine ring (Scheme 7) and finally complete the synthesis of hyrtiazepine **27**.

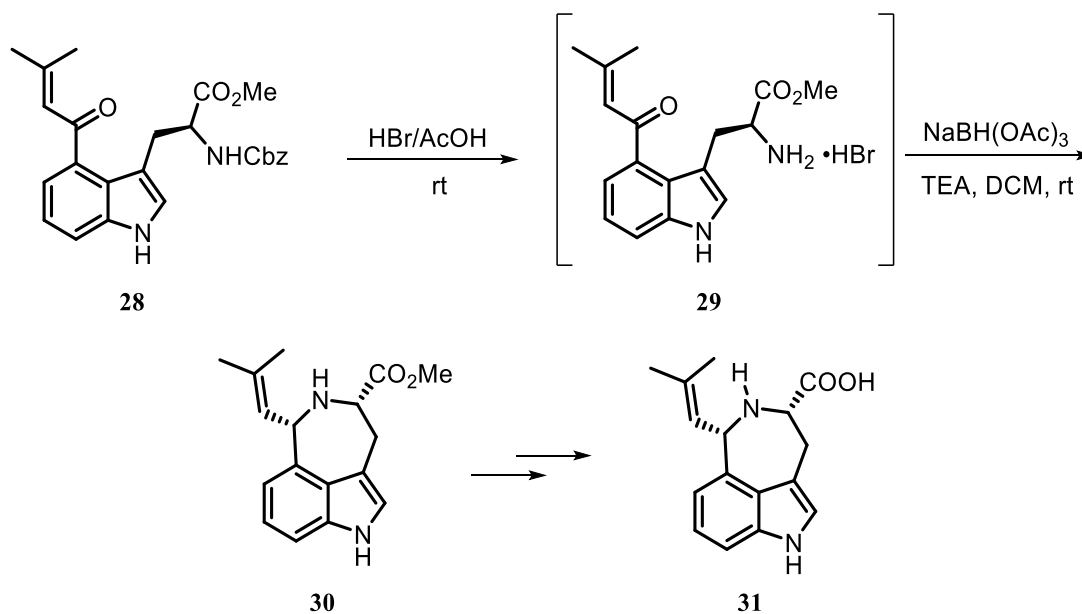
Scheme 7: Synthesis of Hyrtiazepine by Ito *et al.*





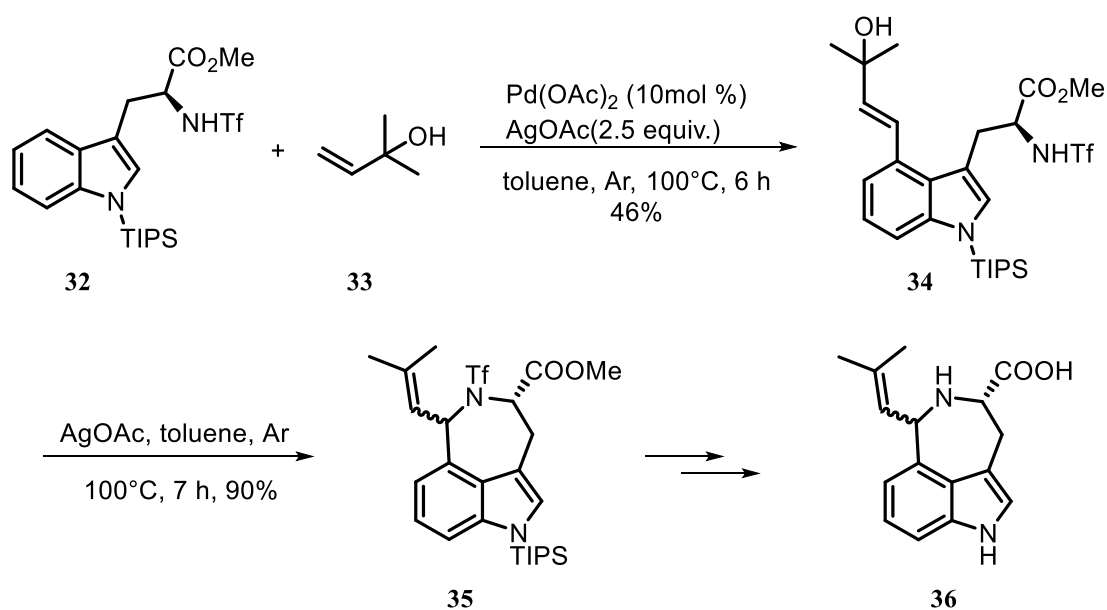
Later, a similar intramolecular reductive amination of ketone using $\text{NaBH}(\text{OAc})_3$ at room temperature was utilized to complete the synthesis of clavicipitic acid by Tahara and coworkers (Scheme 8).⁴⁶

Scheme 8: Synthesis of Clavicipitic Acid by Tahara *et al.*



Liu and coworkers⁴⁷ performed olefination at the C₄ position of tryptophan derivative **32** via a palladium catalyzed C-H activation and finally a silver acetate catalyzed allylic amination to complete the synthesis of clavicipitic acid **36** (Scheme 9).

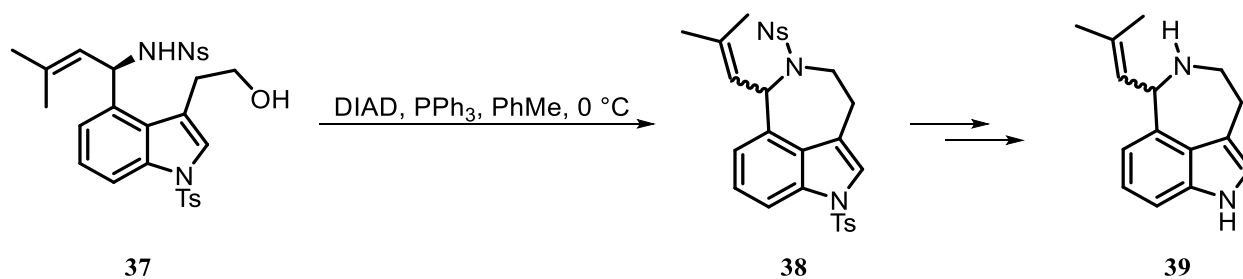
Scheme 9: Liu's Synthesis of Clavicipitic Acid



1.4.3 Syntheses via 'c' Bond Formation

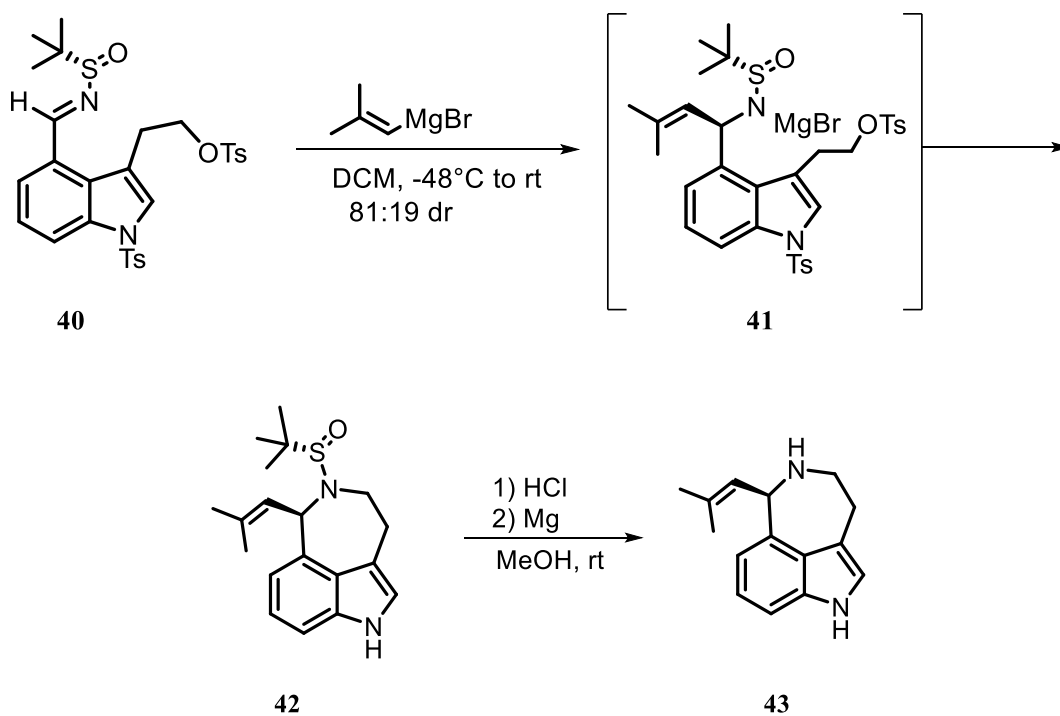
Stoltz group⁴⁸ in 2008 used Mitsunobu reaction of substituted indole **37** to assemble the azepine ring (Scheme 10) to complete the synthesis of aurantioclavine **39**.

Scheme 10: Synthesis of Aurantioclavine by Stoltz *et al.*



Similarly, Ellman *et al.*⁴⁹ utilized the imine precursor **40** which underwent Grignard addition sequence to afford azepinoindole core to complete the synthesis of aurantioclavine **43** (Scheme 11).

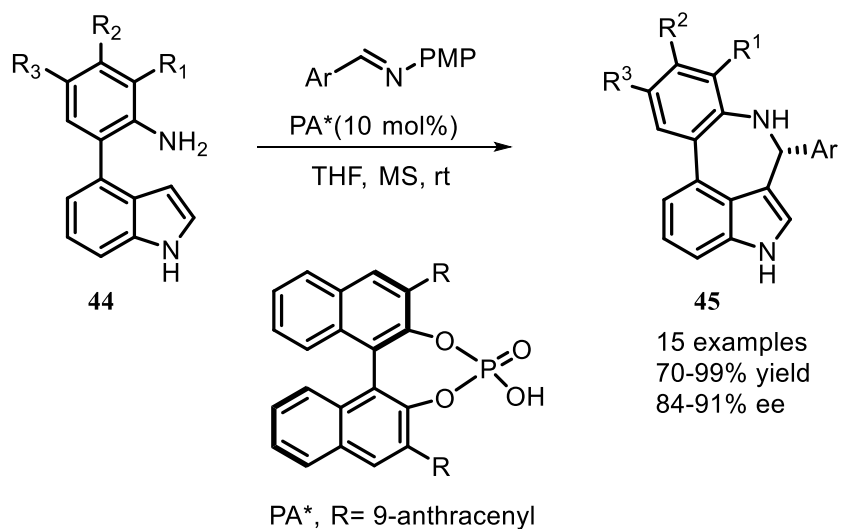
Scheme 11: Synthesis of Aurantioclavine by Ellman *et al.*



1.4.4 Cyclization at 3-Position of Indole

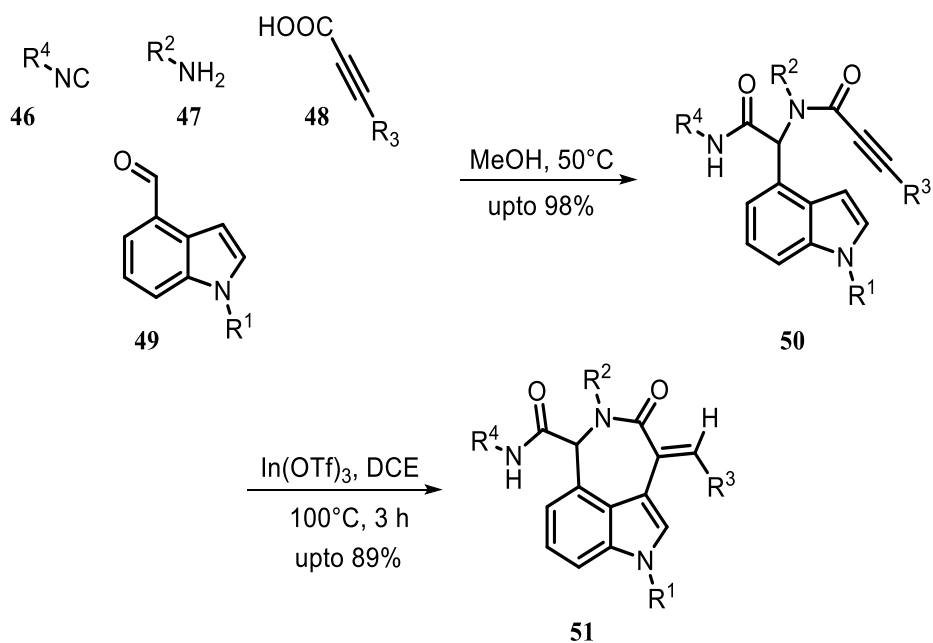
Cheng and coworkers⁵⁰ utilized chiral phosphoric acid catalyzed asymmetric Pictet-Spengler type reaction to close the azepine ring forming the azepinoindole. The method was used successfully to obtain many azepinoindole analogs with high enantioselectivity (Scheme 12).

Scheme 12: Chiral Phosphoric Acid Catalyzed Cyclization



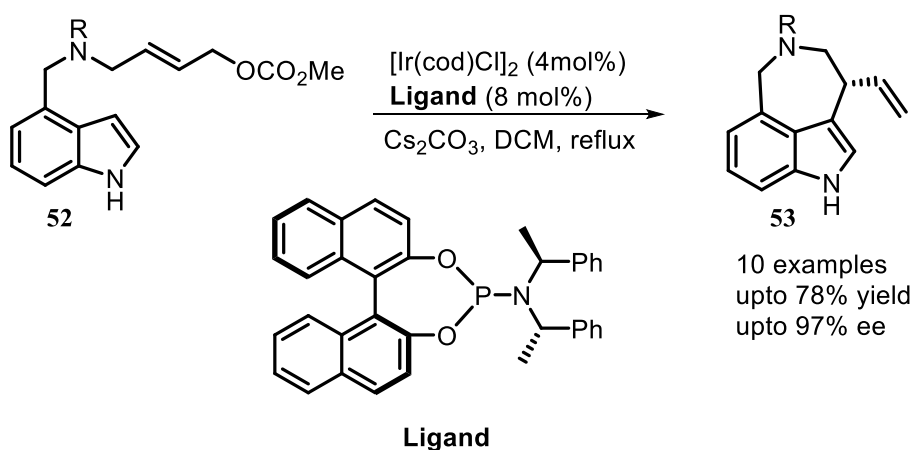
Kumar *et al.*⁵¹ reported the synthesis of azepinoindoles by post-Ugi indium(III)-mediated regioselective intramolecular hydroarylation reaction (Scheme 13).

Scheme 13: Indium Triflate Catalyzed Cyclization



Xu and coworkers⁵² described diversity-oriented synthesis via allylic alkylation reactions where iridium catalyzed pathway provided azepinoindoles selectively (Scheme 14).

Scheme 14: Iridium Catalyzed Cyclization

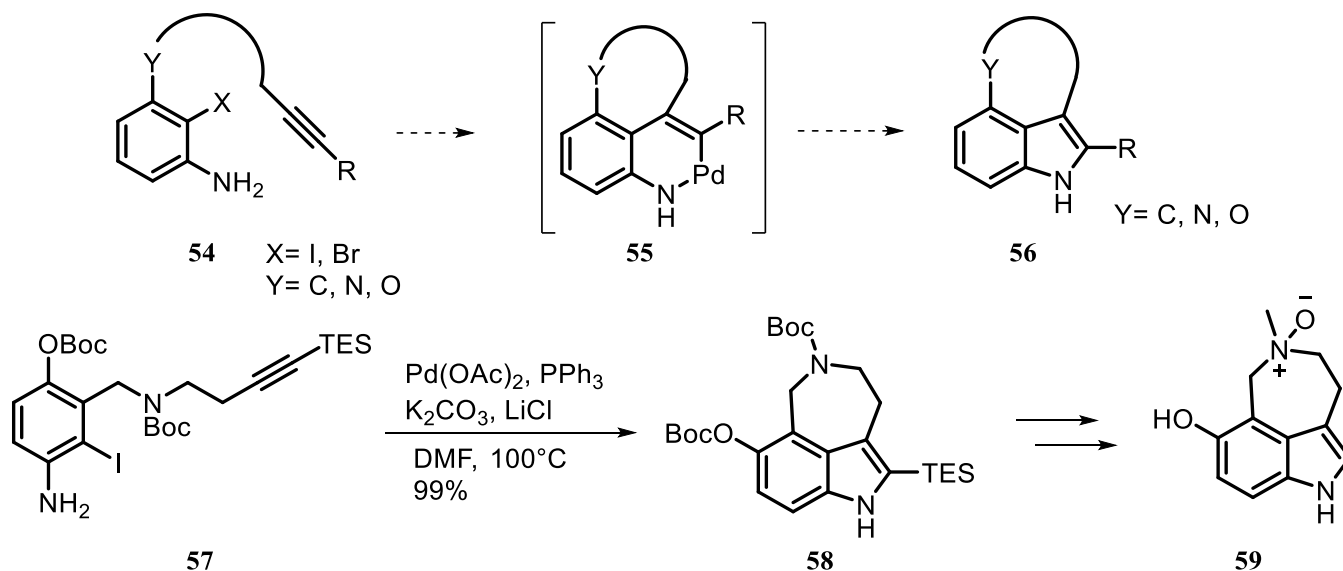


1.4.5 Synthesis via Sequential ‘e’ and ‘f’ or ‘b’, ‘e’ and ‘f’ Bond Formation

The strategies described above, and many others utilize preassembled indole unit as the starting material. Sequential cyclizations forming the ‘e’ and ‘f’ bonds or ‘b’, ‘e’ and ‘f’ bonds have also been reported. The latter methodologies employ functionalized benzene rings as the starting materials and, probably offer more flexible routes to a variety of functionalized analogs.

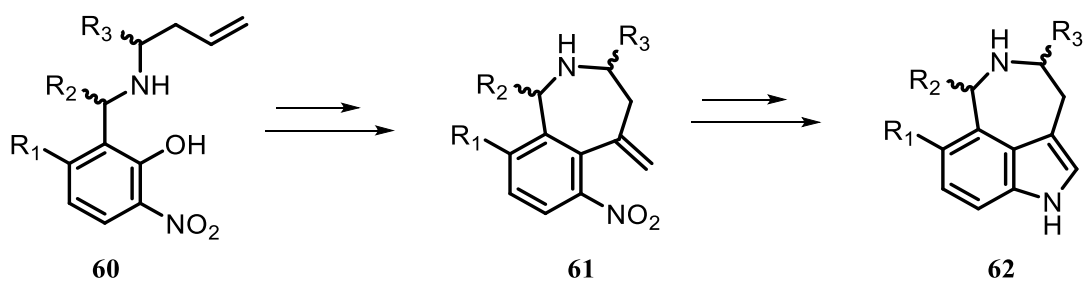
In 2013, Jia and coworkers⁴¹ reported intramolecular Larock indolization reaction to synthesize azepinoindole nucleus. Starting from tetrasubstituted iodoaniline **57** as cyclization precursor, the authors revealed a very efficient way to synthesize 3,4-fused azepinoindoles directly. The method was successfully used to complete the synthesis of fargesine **59**.

Scheme 15: Intramolecular Larock Indole Synthesis



Söderberg *et al.*²⁵ used the stepwise cyclization strategy to form the azepine ring via intramolecular Mizoroki-Heck reaction followed by *N*-heterocyclization to form the azepinoindole. The strategy was successfully used for the total synthesis of cimitrypazepine, fargesine and Hyrtioreticulins C & D.

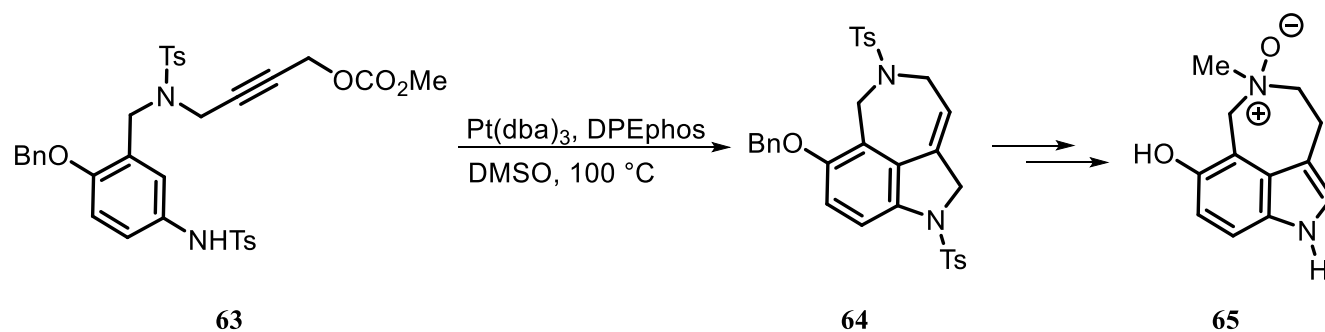
Scheme 16: Söderberg's Sequential Cyclization



Recently, Nemoto *et al.*⁵³ described the synthesis of 3,4-fused tricyclic indole structure based on the platinum-catalyzed intramolecular Friedel-Crafts-type C–H coupling–allylic amination cascade and used it to complete the total synthesis of fargesine (Scheme 17).

Compared to Jia *et al.* who used tetrasubstituted iodoaniline derivative, they used trisubstituted aniline derivative for the synthesis.

Scheme 17: Nemoto's Synthesis of Fargesine



Chapter 2

Short Syntheses of Cimitrypazepine and Fargesine

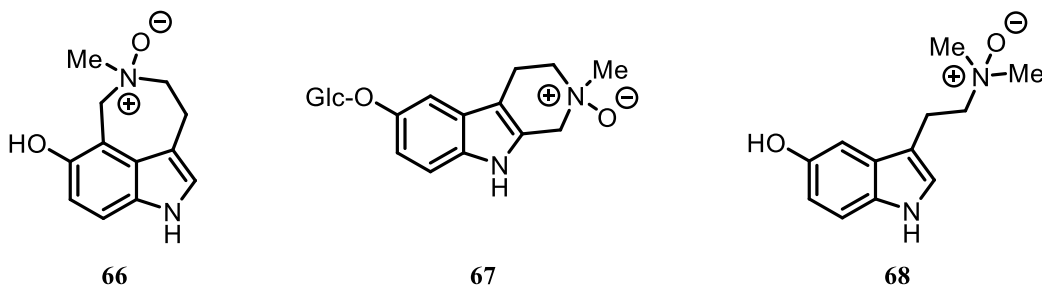
2.1 Introduction to Cimitrypazepine and Fargesine	19
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2.1 Introduction to Cimitrypazepine and Fargesine

Cimitrypazepine was extracted from the roots of black cohosh *Cimicifuga racemosa* in 2012. The roots/rhizomes of black cohosh have traditionally been used by Native Americans for treating a variety of medical conditions such as colds, rheumatism as well as for alleviating menopausal symptoms such as hot flashes. Because of the risks associated with hormone replacement therapy, black cohosh preparations have become popular dietary supplements among women seeking alternative treatments for menopausal complaints. Nikolić and coworkers³¹ confirmed the azepinoindole structure of cimitrypazepine by comparing the mass spectrometric fragmentation of natural and synthetic samples of the alkaloid.

Traditional Chinese folk medicine has employed the fruits of *Evodia fargesii* as a cough suppressant as well as an analgesic for stomach aches. Three new *N*-oxide alkaloids were isolated from the roots and stems of the plant in 2006 (Figure 6).³⁰ Among those, the tricyclic *N*-oxide alkaloid fargesine **66** was identified to be an azepino[5,4,3-*cd*]indole. Even though the components from the extracts of *Evodia* species have been found to be biologically active, biological activity of fargesine has not been studied so far.

Figure 6: Structure of *N*-Oxide Alkaloids from *Evodia fargesii*

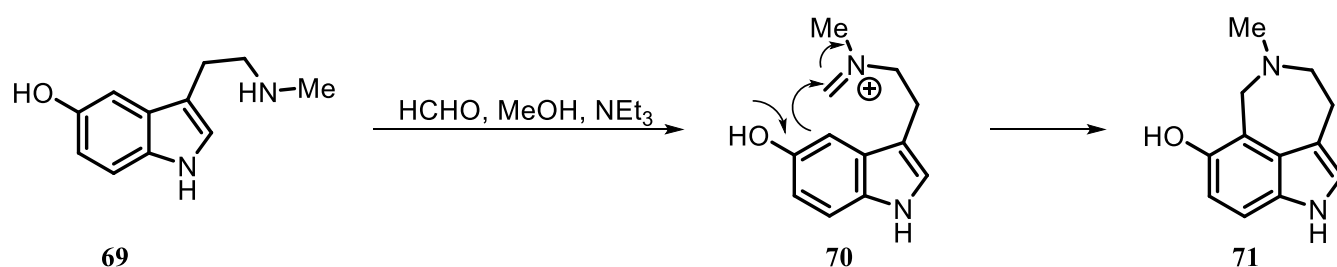


2.2 Literature Synthesis of Cimitrypazepine and Fargesine

2.2.1 Nikolić's Synthesis of Cimitrypazepine

Nikolić *et al.*³¹ reported the synthesis of cimitrypazepine **71** using a Pictet-Spengler type cyclization of *N*-methylserotonin **69** and formaldehyde as the key azepine ring-forming step. The authors reported ¹H-NMR data and also compared the mass spectrometric data of the synthetic cimitrypazepine with the natural compound.

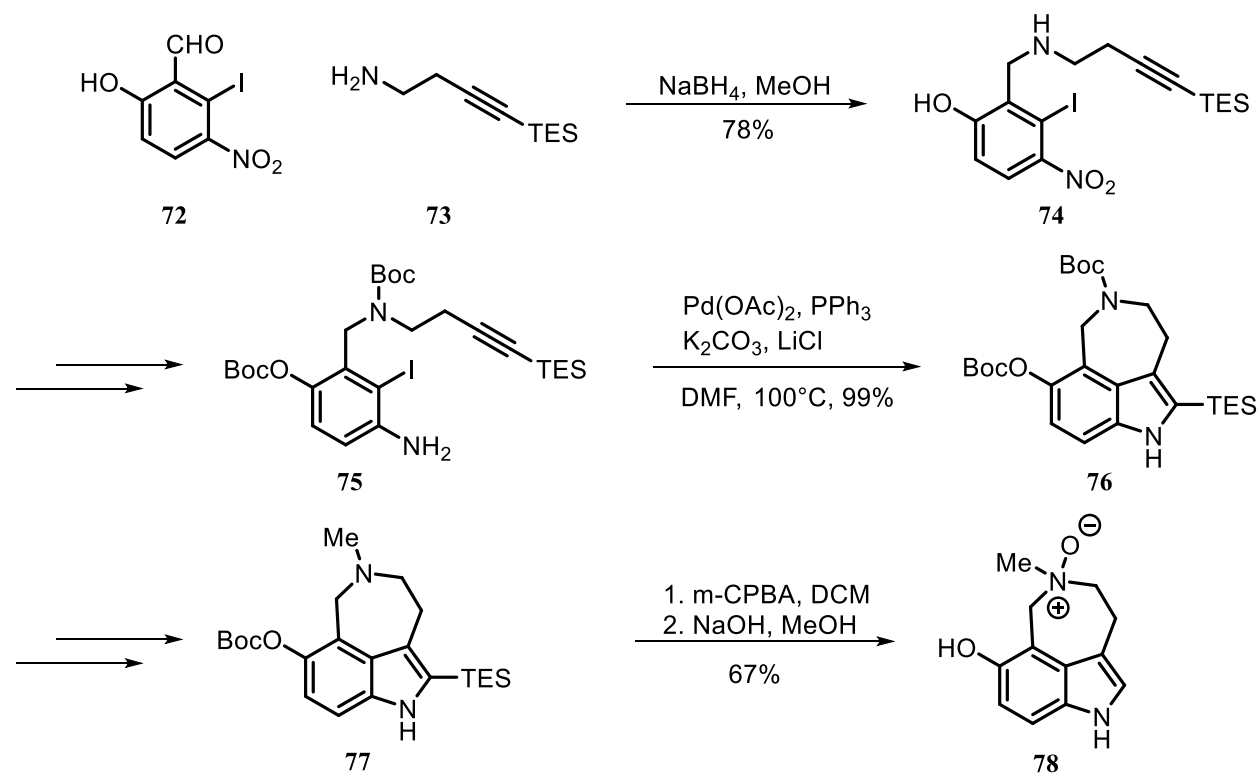
Scheme 18: Biomimetic Synthesis of Cimitrypazepine



2.2.2 Jia's Synthesis of Fargesine

In 2013, Jia and coworkers⁴¹ developed an efficient strategy to synthesize fused tricyclic indoles from substituted 2-halogenanilines via the palladium-catalyzed intramolecular Larock indolization process and used it to complete the first total synthesis of fargesine (Scheme 19). The reductive amination between benzaldehyde and primary amine afforded the secondary amine adduct **74**. Protection of both hydroxy and amine functional groups using Boc₂O followed by reduction of nitro group provided the cyclization precursor **75** in good yield. The key Larock indolization of aniline **75** gave the tricyclic azepinoindole which after stepwise deprotection, *N*-methylation and *N*-oxidation sequence provided fargesine **78**.

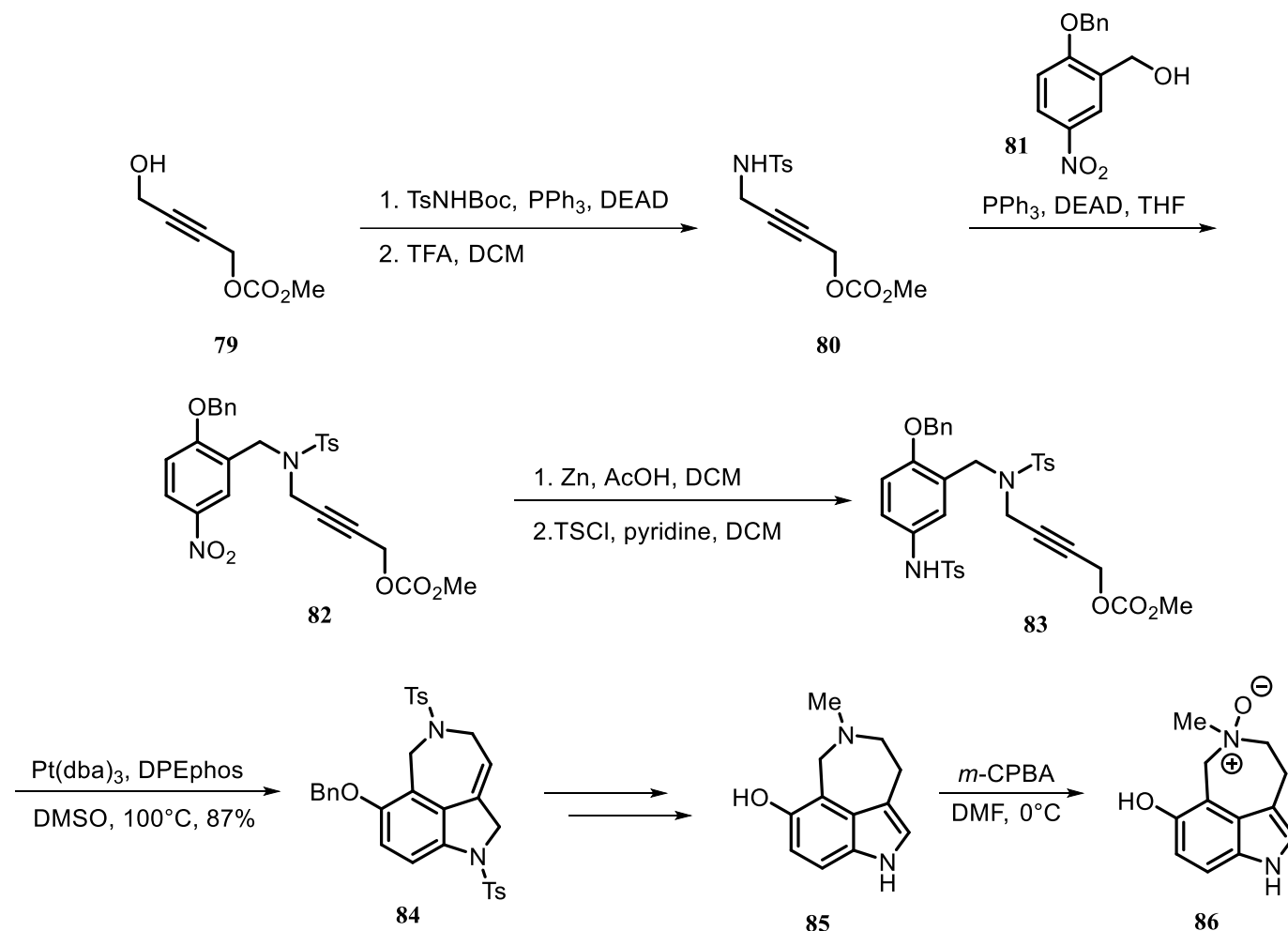
Scheme 19: Jia's Synthesis of Fargesine



2.2.3 Nemoto's Synthesis of Cimitrypazepine and Fargesine

Cimitrypazepine and fargesine were also synthesized recently by Nemoto and coworkers⁵³ using a platinum-catalyzed intramolecular Friedel-Crafts type C-H coupling-allylic amination cascade (Scheme 20). The cyclization precursor **83** was synthesized using two consecutive Mitsunobu reactions followed by Zn-mediated reduction of nitro group. The platinum-catalyzed intramolecular Friedel-Crafts type C-H coupling-allylic amination cascade provided the tricyclic indoline **84**, which after TFA mediated isomerization, Na-naphthalide reduction, *N*-methylation and debenzylolation sequence gave cimitrypazepine **85**. Finally, *m*-CPBA mediated *N*-oxidation of cimitrypazepine afforded fargesine **86**.

Scheme 20: Nemoto's Synthesis of Cimitrypazepine and Fargesine



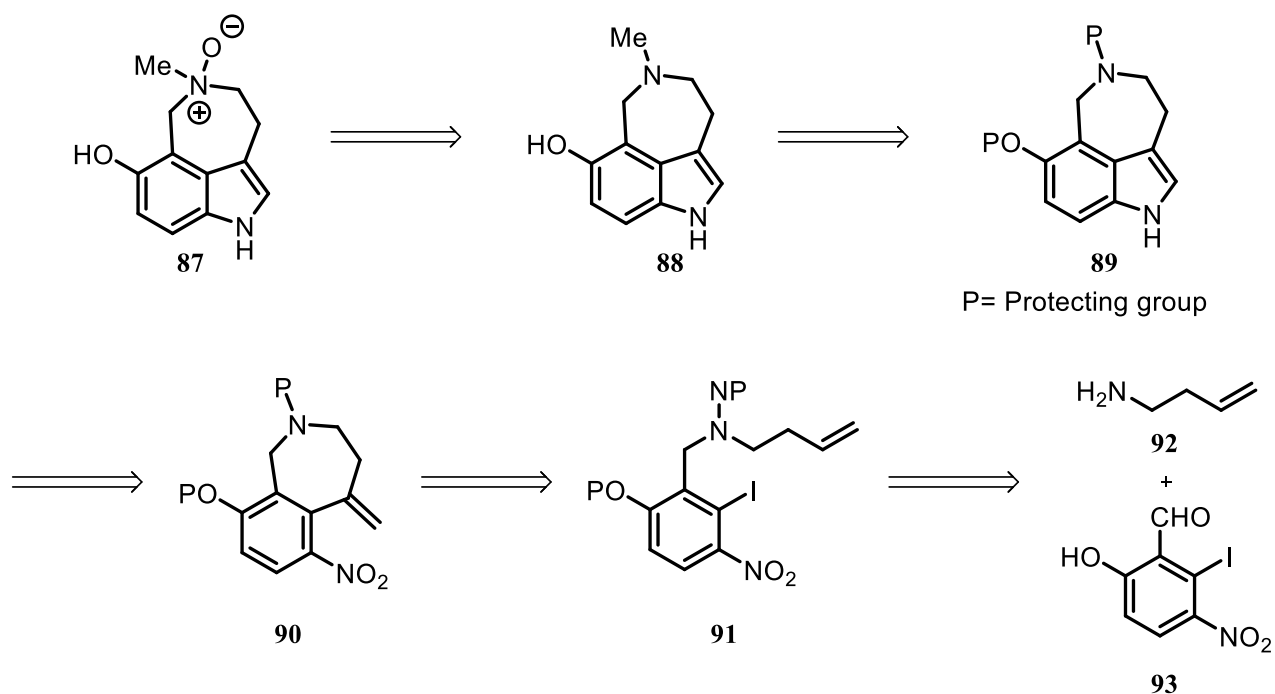
2.3 Short Syntheses of Cimitrypazepine and Fargesine

The unique structure of fargesine featuring an azepino[5,4,3-*cd*]indole core and *N*-oxide function in the azepine ring inspired us to commence a synthetic study. The goal of the synthesis was to highlight the use of the Watanabe-Cenini-Söderberg palladium-catalyzed reductive *N*-heterocyclization as the key step to assemble the indole ring at the later stage of natural products synthesis.

2.3.1 Retrosynthetic Analysis

The intriguing structure of cimitrypazepine and fargesine allowed us to propose a relatively concise synthetic route (Scheme 21). It was envisioned that fargesine **87** could result from *N*-oxidation of cimitrypazepine **88**. Cimitrypazepine **88**, in turn, could be achieved by *N*-methylation of the azepine ring of *N*-protected amine **89**. The indole core of **89** could be prepared through Watanabe-Cenini-Söderberg reductive *N*-heterocyclization of nitroaromatic **90**. Intramolecular Heck reaction of terminal alkene **91** would give the desired reductive *N*-heterocyclization precursor **90**. The terminal alkene **91** could be prepared by a reductive amination of known aldehyde **93** and 4-amino-1-butene **92**.

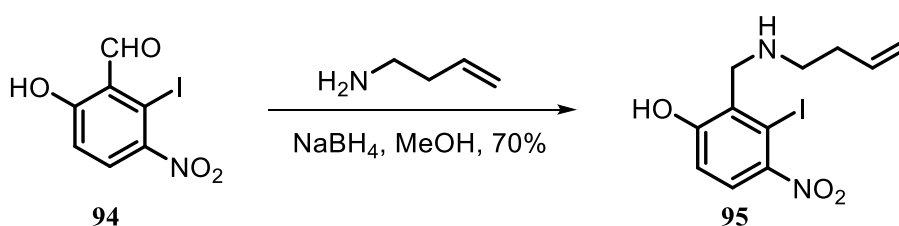
Scheme 21: Proposed Retrosynthetic Outline for Cimitrypazepine and Fargesine



2.3.2 Results and Discussion

6-Hydroxy-2-iodo-3-nitrobenzaldehyde (**94**),⁵⁴ readily prepared from commercially available 4-hydroxy-2-iodo-1-nitrobenzene, served as the starting point for the synthesis of both cimitrypazepine and fargesine (Scheme 22). Reductive amination of **94** using 4-amino-1-butene and sodium borohydride afforded the expected product **95** in good yield.

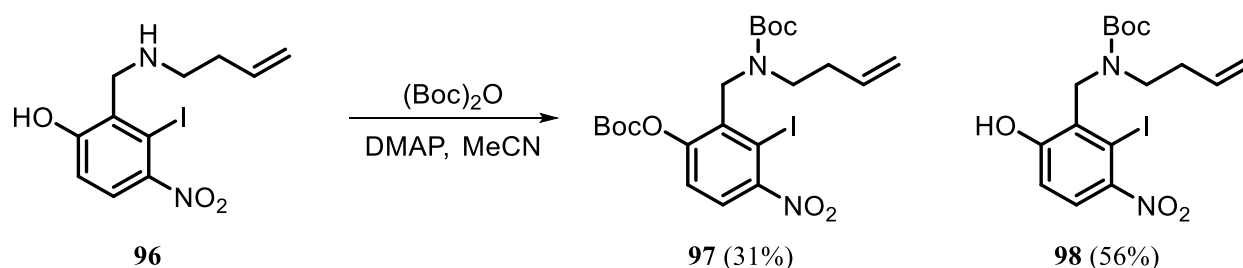
Scheme 22: Reductive Amination of 6-Hydroxy-2-iodo-3-nitrobenzaldehyde



The next goal was to assemble the azepine ring from **95**. Treatment of compound **95** under typical Heck conditions, using a palladium diacetate – tri(*o*-tolyl) phosphine catalyst system in triethylamine as the solvent and stirring at 125 °C, did not furnish any observable amount of the anticipated bicyclic product. This was probably due to the coordination of -NH and -OH group with the catalyst system inhibiting the desired coordination with the alkene moiety. Therefore, both the hydroxy and the amino group in **95** were protected by reaction with di-*t*-butyldicarbonate ((Boc)₂O) in the presence of 4- (*N*, *N*-dimethylamino)pyridine (DMAP). The starting material **95** was cleanly converted into a single new compound (by TLC). The anticipated di-protected compound **97** was the only aromatic compound seen in the ¹H NMR spectrum of the crude reaction mixture. However, upon purification by chromatography on silica gel, the *O*-deprotected compound **98** was isolated as the major product, in addition to **97** (Scheme 23). It was speculated that the -*O*-Boc group readily falls off during purification under standard silica gel chromatography conditions. However, it was possible to increase the

percentage of di-protected compound **97** upon treatment of **98** using the same reaction conditions. The *N*-Boc group was intended to serve a dual purpose, lowering the coordination ability of the nitrogen, at times a problem in intramolecular Heck reactions, and as a source of the azepine *N*-methyl group after reduction. In our case, protection of the amine was crucial for the Heck reaction to occur.⁵⁵

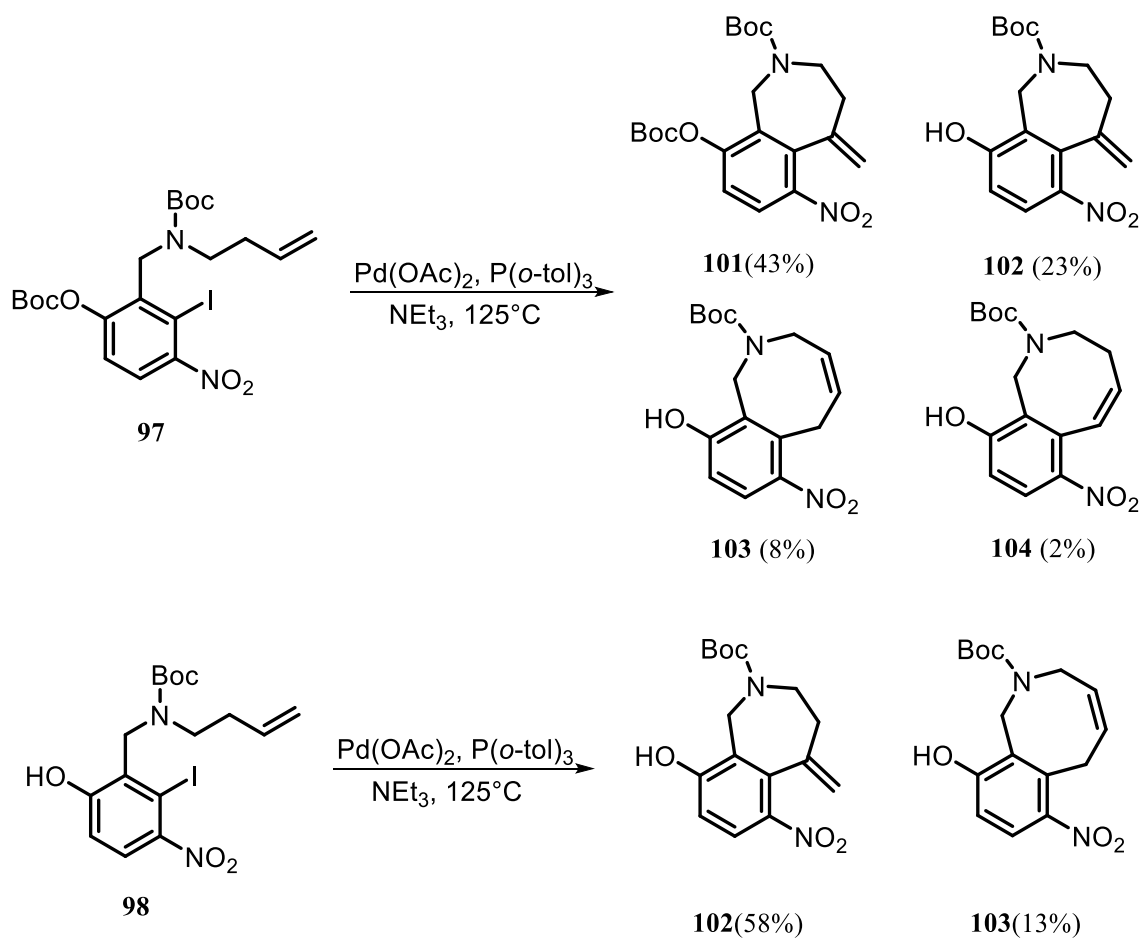
Scheme 23: Synthesis of *O*-Boc and *N*-Boc Protected Amines **97 and **98**.**



Intramolecular Heck reactions were attempted using both **97** and **98** in order to evaluate the need for *O*-protection. Di-protected compound **97** was completely consumed after 3.5 h as observed by TLC. Work up and careful purification by chromatography gave four different products (Scheme 24). Two 2-benzazepines, the di-*O*, *N*-Boc protected compound **101** and the *N*-Boc protected compound **102**, were isolated as the major products. In addition, minor amounts of two 2-benzazocines (**103** and **104**) differing in the position of the unsaturation in the eight-membered ring were also obtained. The latter two compounds had lost the *O*-Boc group during the reaction or upon purification of the crude reaction mixture. Intramolecular Heck reactions affording mixtures of 2-benzazepines and 2-benzazocines have previously been reported.⁵⁶ It should be noted that the Heck reaction of **97** was unpredictable and varying ratios and yields of products were obtained from seemingly identical reaction conditions and concentrations. The result shown in Scheme 24 represents the highest isolated yield of **101** and **102** obtained in

several cyclizations of **97**. In comparison to the reaction of **97**, cyclization of **98** was more consistent but gave a slightly lower isolated yield of the 2-benzazepine product **102** (relative to **101+102**, 66%) and a slightly higher yield of 2-benzazocine **103**.

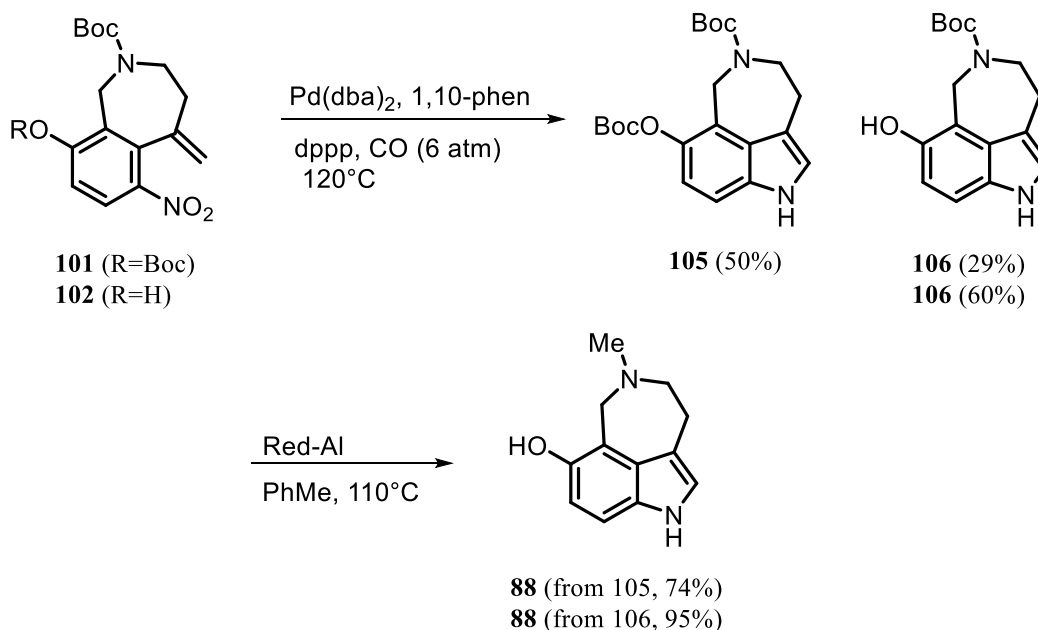
Scheme 24. Synthesis of 2-Benzazepines 101 and 102 and Benzazocines 103 and 104.



Palladium catalyzed reductive *N*-heterocyclization of **101** using a bis(dibenzylideneacetone)palladium-1,3-bis(diphenylphosphino)propane-1,10-phenanthroline catalyst system in the presence of carbon monoxide ($p_{\text{CO}} = 6 \text{ atm}$, 120°C) in *N,N*-dimethylformamide, furnished the di-*N,O*-protected azepino[5,4,3-*cd*]indole **105** in addition to

the *N*-protected analogue **106** in 79% total yield (Scheme 25). Treatment of compound **102** using the same reagents and reaction conditions also gave **106** in a somewhat lower isolated yield. Finally, upon treatment of **105** with sodium bis(2-methoxyethoxy) aluminum hydride (Red-Al) in toluene at reflux, the *O*-Boc group was removed and the *N*-Boc group of **105** was reduced to a methyl group affording **88** (cimitryptazepine). Alkaloid **88** was also isolated in excellent yield from Red-Al reduction of **106**. All analytical data including ^1H and ^{13}C NMR, IR, HRMS, and melting point of synthetic cimitryptazepine were identical to the literature values of the compound isolated and synthesized by Nikolic *et al.*³¹

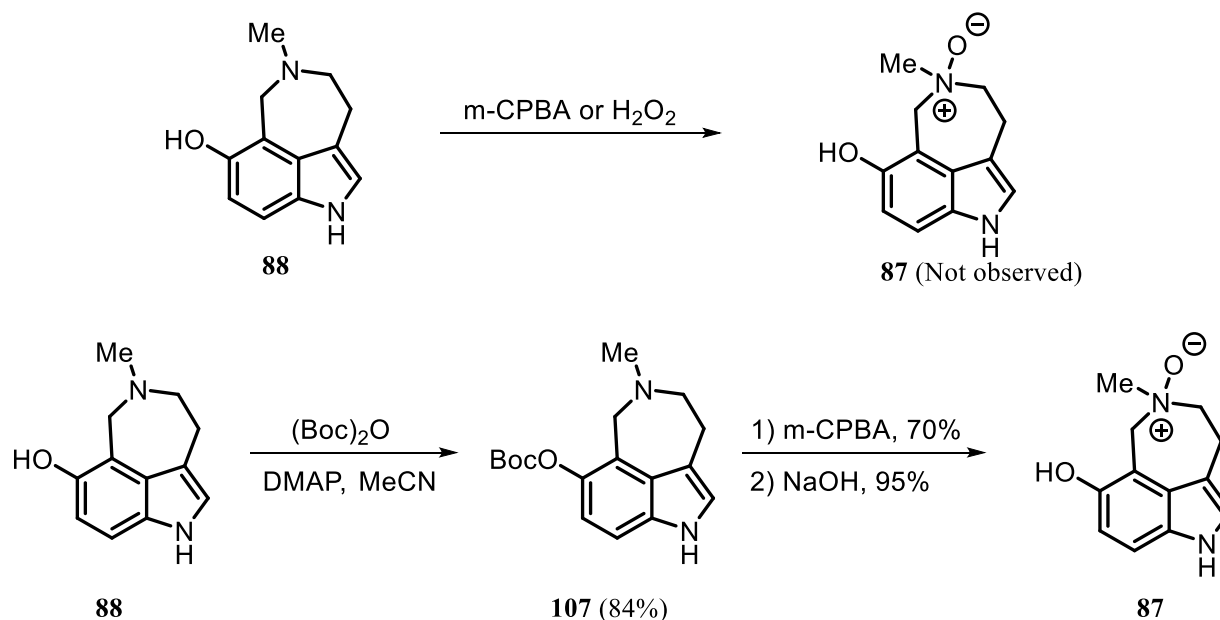
Scheme 25. *N*-Heterocyclization and Reduction to Give Cimitryptazepine 88



Direct oxidation of the azepine-nitrogen of **88** using *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane⁵⁷ or hydrogen peroxide – ammonium hydrogen carbonate in water did not furnish fargesine; instead intractable mixtures were obtained in all attempted reactions. In place of a direct oxidation of **88** to fargesine, we decided to intercept an intermediate reported in the

previous synthesis of fargesine.⁴¹ Thus, cimitrypazepine **88** was *O*-Boc-protected to give **107** in excellent yield. This compound has previously been oxidized and deprotected using *m*-CPBA and sodium hydroxide, respectively, to afford fargesine **87**.

Scheme 26. Synthesis of Fargesine **87**



2.4 Conclusions

A concise linear total syntheses of the naturally occurring azepino[5,4,3-*cd*]indoles, cimitrypazepine and fargesine has been completed utilizing an intramolecular Heck reaction forming the azepine ring and Watanabe-Cenini- Söderberg reductive *N*-heterocyclization building the pyrrole ring of the indole as key steps. The flexibility offered by our intramolecular Heck reaction to form the azepine ring and late stage reductive *N*-heterocyclization opens the possibility of using the strategy in other synthesis of other azepinoindole alkaloids.

Chapter 3

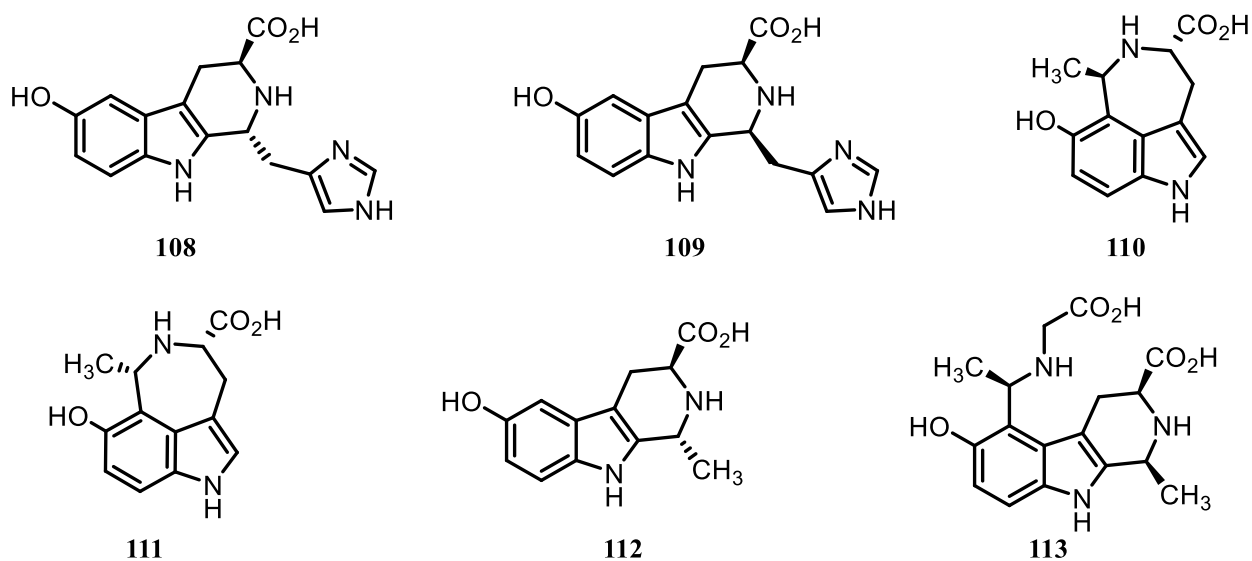
Syntheses of Hyrtioreticulins C & D

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3.1 Introduction to Hyrtioreticulins C & D

Marine sponges of the genus *Hyrtios* are known to be rich sources of structurally diverse natural products such as alkaloids, sesterterpenes and macrolide with significant cytotoxic and antimicrobial activities. Out of six hyrtioreticuline analogs (A-F, **108-113**) isolated so far from the *Hyrtios* species (Figure 7),^{58,59} Hyrtioreticulins A and B inhibited ubiquitin-activating enzyme (E1). Hyrtioreticulins C & D were isolated as diastereomeric azepinoindole alkaloids from the marine sponge *Hyrtios reticulatus*, which was collected in Indonesia by Tsukamoto and co-workers.⁵⁸ Even though the detailed biological study of hyrtioreticulins C & D has not been reported, these azepinoindole alkaloids are attractive synthetic targets as they resemble aurantioclavine and clavicipitic acid. The first synthesis of hyrtioreticulins C and D was reported by Abe and Yamada^{43c} in 2017 wherein a Pictet-Spengler cyclization was employed as the key step.

Figure 7: Hyrtioreticulins A-F (108-113) Isolated From *Hyrtios reticulatus*

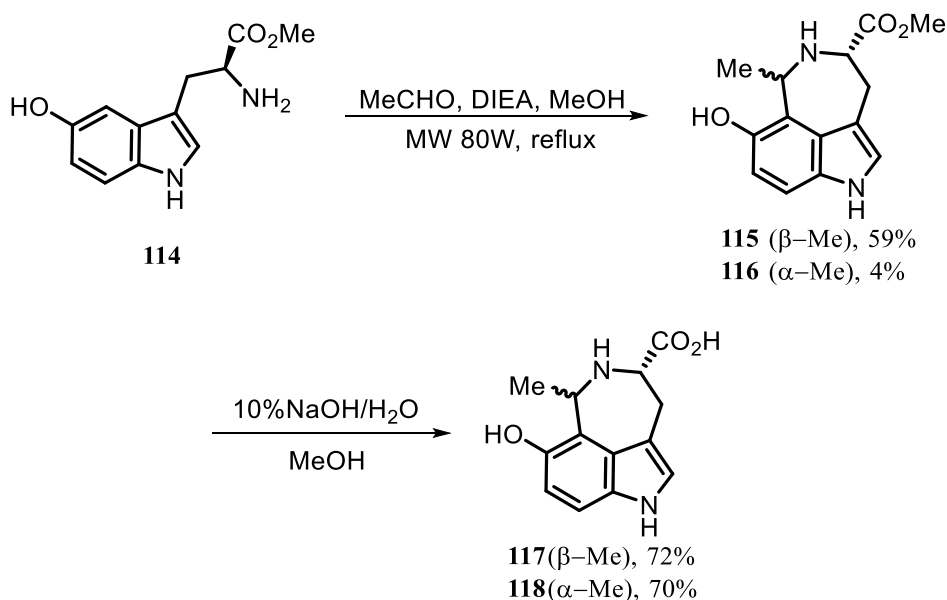


3.2 Previous Synthesis of Hyrtioreticulins C & D

3.2.1 Abe and Yamada Synthesis

In 2017, Abe and Yamada^{43c} reported the first total syntheses of hyrtioreticulins C & D. Their biomimetic synthesis featured an unprecedented base-promoted C-4 Pictet-Spengler reaction of tryptophan. Microwave irradiation of 5-hydroxytryptophan **114** with 3 equivalents of acetaldehyde under basic condition selectively formed azepino[5,4,3-*cd*]indoles having trans isomer as the major product (Scheme 27). Basic hydrolysis of azepinoindoles **115** and **116** gave hyrtioreticulins C & D (**117** and **118**), respectively.

Scheme 27: First Synthesis of Hyrtioreticulins C & D



3.3 Total Syntheses of Hyrtioreticulins C & D

Abe and Yamada synthesis utilized the preformed tryptophan which possessed a pre-installed indole ring as the starting material. Our goal was to elaborate the use of Watanabe-

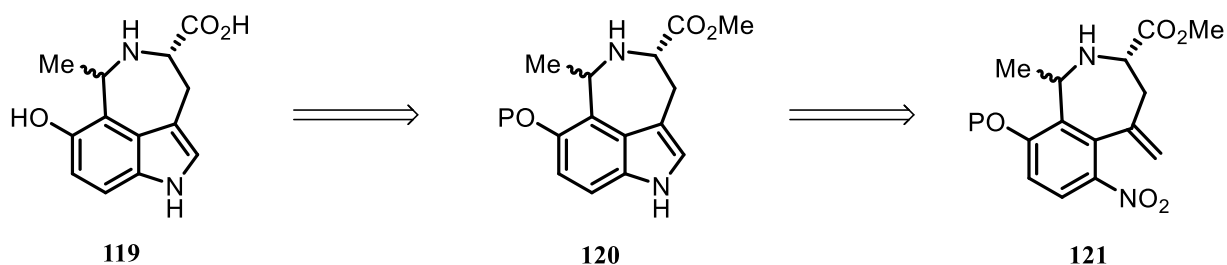
Cenini-Söderberg reductive *N*-heterocyclization reaction as an efficient tool for a late stage indole ring formation.

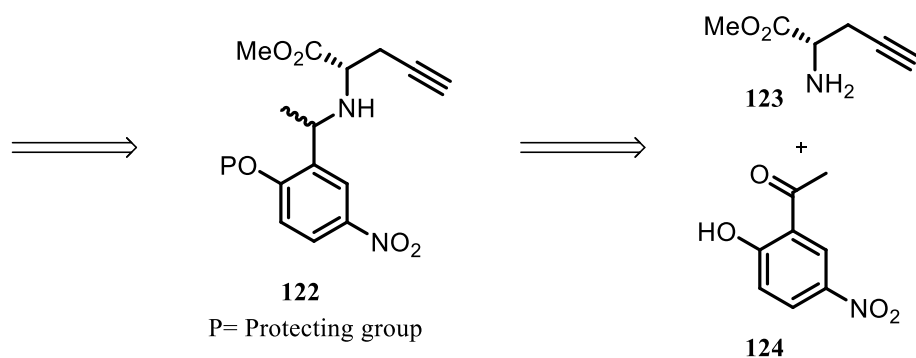
3.3.1 Retrosynthetic Analysis

The resemblance of hyrtioreticulins with cimitrypazepine and fargesine previously synthesized in our lab²⁵ prompted us to propose a relatively similar synthetic route (Scheme 28). In order to explore the versatility of our terminally unsaturated *N*-tethered cyclization precursor, our initial synthetic design was inspired from the work of Zhang *et al.* that utilized an efficient rhodium(III)-catalyzed intramolecular hydroarylation of alkynes.⁶⁰ The method would serve as an alternative route for installing the key azepine ring and thereby provide a straight forward route, after reductive *N*- heterocyclization, to the tricyclic azepinoindole.

It was envisioned that the hyrtioreticulins **119** could result from protecting group manipulation of **120**. The indole core of **120** could be prepared through Watanabe-Cenini-Söderberg reductive *N*-heterocyclization of nitroaromatic **121**. It was speculated that the rhodium(III)-catalyzed intramolecular hydroarylation of alkynes proposed by Zhang and coworkers could be used for terminal alkyne **122** to give the desired reductive cyclization precursor **121**. The terminal alkyne **122** could be prepared by reductive amination of known acetophenone derivative **124** and propargyl glycine methyl ester **123**.

Scheme 28: Proposed Retrosynthetic Outline for Hyrtioreticulins

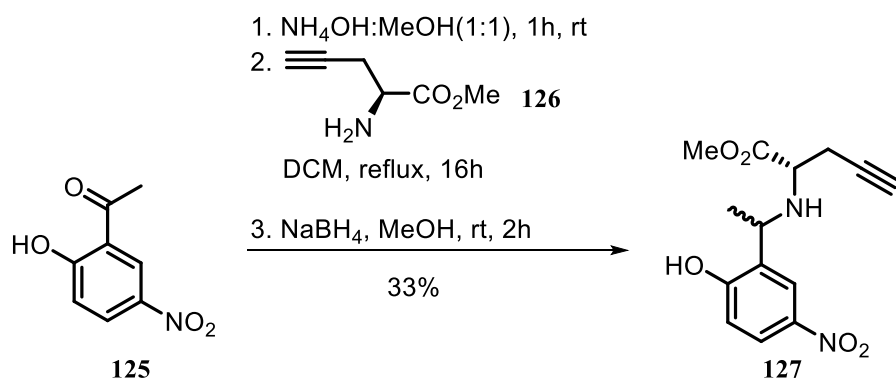




3.3.2 Results and Discussion

The forward synthesis of hyrtioreticulins started from commercially available 2-hydroxy-5-nitroacetophenone. Under the optimized conditions, transimination of *in situ* generated primary ketimine of 2-hydroxy-5-nitroacetophenone **125** with amine **126** followed by sodium borohydride reduction of the corresponding imine gave the new racemic amine **127** in 33% overall yield (Scheme 29).

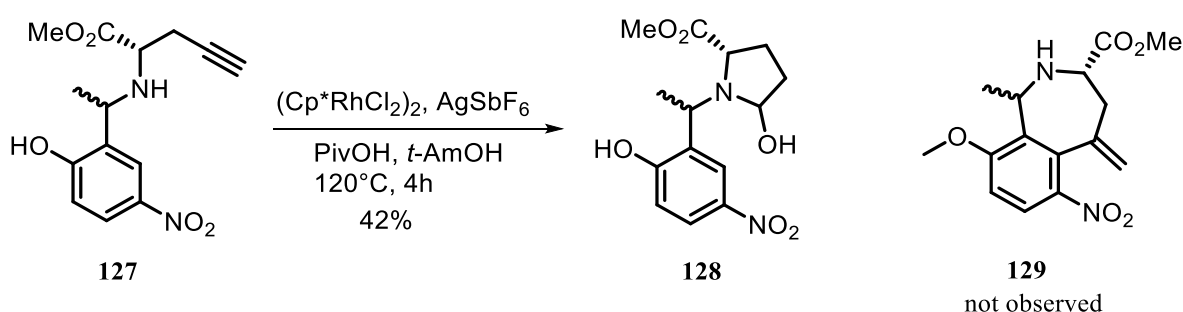
Scheme 29: Indirect Reductive Amination to Form **127**



Amine **127** was then subjected to Rh(III)-catalyzed intramolecular annulation as described by Zhang *et al.*⁶⁰ Unfortunately, the desired 2-benzazepine **129** was not detected even after varied reaction conditions; instead an undesired cyclization product **128** was isolated as the sole product in 42% yield (Scheme 30). The product **128** was also isolated in about 30% yield

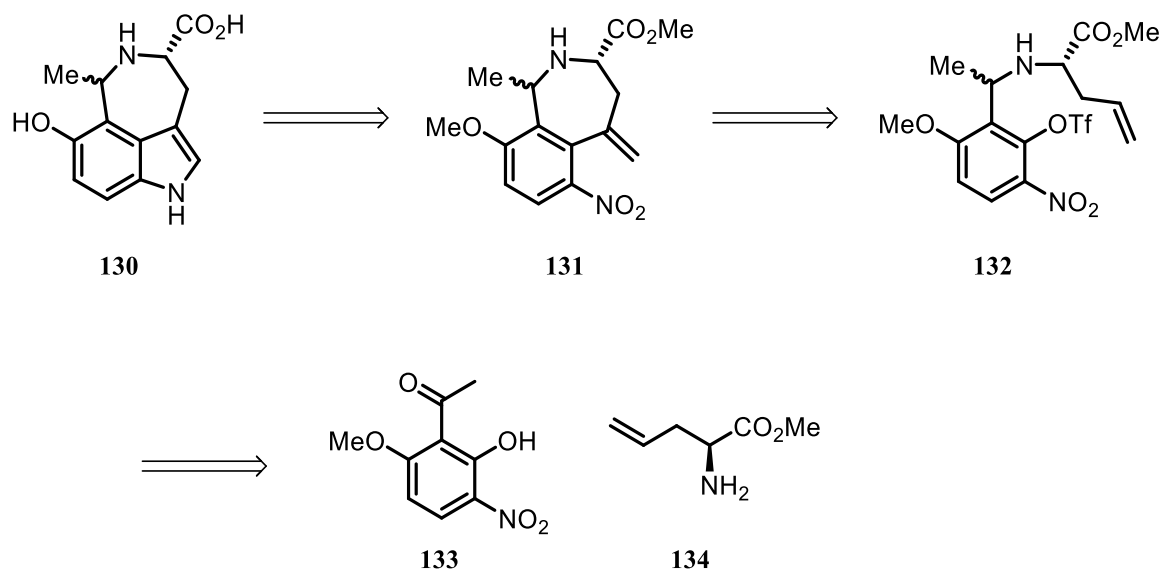
under similar reaction conditions without the rhodium catalyst. The isolated product probably resulted from an intramolecular hydroamination of terminal alkyne **127** favoring a *5-endo-dig* cyclization.⁶¹ It was also expected that the unprotected secondary amine in **127** could coordinate with the metal and prevent the otherwise possible C-H activation by the catalyst thereby favoring the formation of **128**.

Scheme 30: Undesired Cyclization of **127**



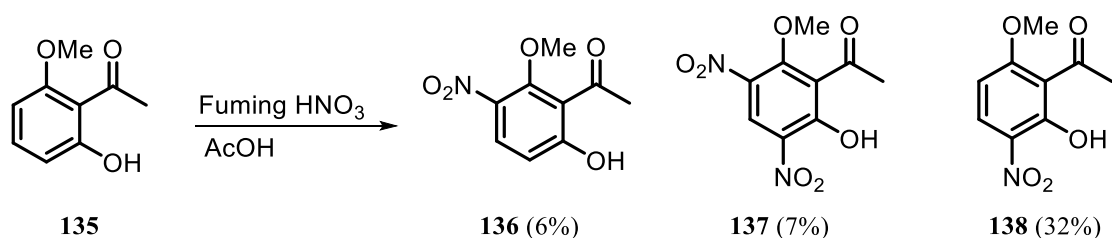
These results prompted us to revisit our synthetic design where the key benzazepine could be obtained using Mizoroki-Heck reaction of terminal alkene as evidenced by our synthesis of cimitrypazepine and fargesine.²⁵ This allowed us to modify our retrosynthetic analysis as shown in scheme 31. It was envisioned that the hyrtioreticulins **130** could result, after the removal of protecting groups, from Watanabe-Cenini-Söderberg reductive *N*-heterocyclization of benzazepine **131**. Intramolecular Mizoroki-Heck reaction of terminal alkene **132** would give the desired reductive *N*-heterocyclization precursor **131**. The terminal alkene **132** could be prepared by reductive amination of known acetophenone derivative **133** and allyl glycine methyl ester **134**.

Scheme 31: Revised Retrosynthetic Outline for Hyrtioreticulins



The alternative synthesis was started from nitration of commercially available 2-hydroxy-6-methoxyacetophenone **135** according to Cushman *et al.*⁶² The authors reported only **138** as the nitration product from **135**. But after careful purification of the crude reaction mixture by chromatography, we were able to isolate three products **136**, **137** and **138** (Scheme 32).

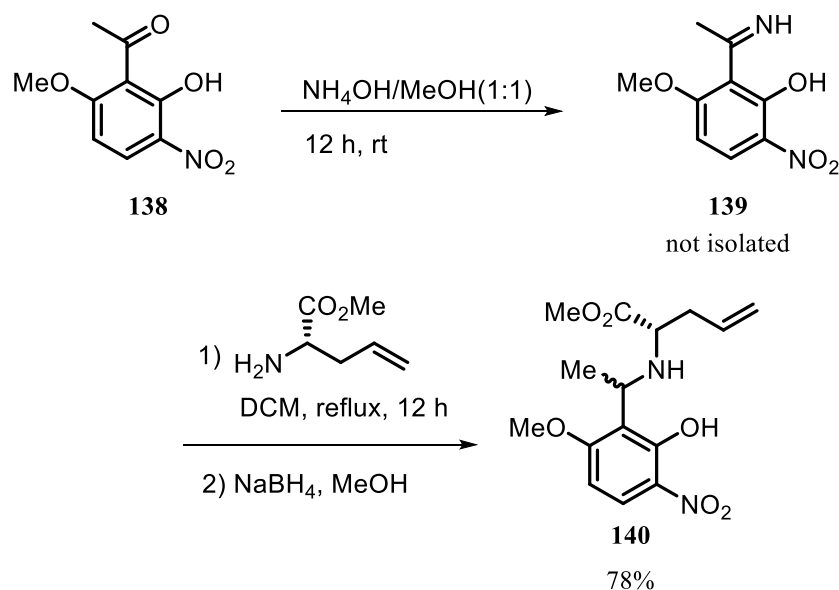
Scheme 32: Nitration of 2-Hydroxy-6-methoxyacetophenone



The next goal was to use the desired **138** to construct the Heck reaction precursor. It should be noted here that direct reductive amination of **138** with allyl glycine methyl ester **134** using a series of reagents (NaBH_4 , NaBH_3CN , TiCl_4 etc.) did not produce the desired product. The ketone **138** was then subjected to trans-amination conditions by treating it with excess

ammonia solution in methanol followed by the amino acid methyl ester before reducing the corresponding imine with sodium borohydride. The product obtained was a racemic mixture **140** in 78% overall yield (Scheme 33).

Scheme 33: Trans-imation of 2-Hydroxy-6-methoxy-3-nitroacetophenone with L-allylglycine Methyl Ester

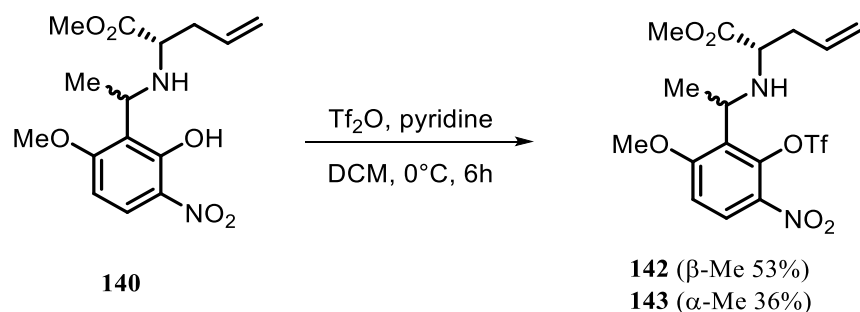


Intramolecular Heck reaction of **140** using one of the standard catalyst systems, palladium diacetate – tri(*o*-tolyl)phosphine – triethyl amine (125 °C)^{25,55} did not furnish any observable amount of the anticipated bicyclic product. Eventually, we decided to adopt an alternative method recently reported by Zhou *et al.*⁶³ The authors described a highly regioselective intermolecular Mizoroki-Heck reaction of aryltriflates with aliphatic olefins leading to the formation of 1,1-disubstituted alkene. To the best of our knowledge, the catalyst system developed by Zhou *et al.* has not been evaluated in intramolecular reactions.

Even though partial separation of the diastereomers of **140** was possible, they were directly reacted with trifluoromethanesulfonic anhydride ($\text{ Tf}_2\text{O}$) and pyridine with the

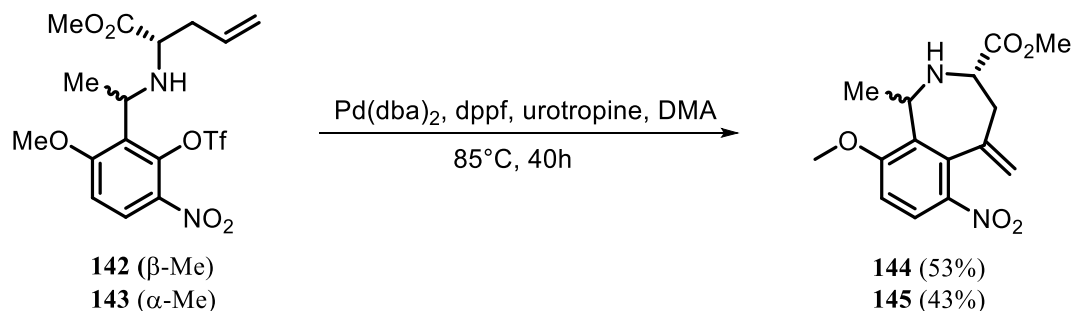
speculation that the corresponding triflates could be separated during purification of the crude product. As expected, the corresponding triflates **142** and **143** were readily separated during purification of the crude reaction mixture with excellent isolated yields (Scheme 34).

Scheme 34: Triflation of Racemic Phenol 140



When the triflates **142** and **143** were subjected to intramolecular Mizoroki-Heck reaction under Zhou's conditions using bis(dibenzylidenacetone)palladium ($\text{Pd}(\text{dba})_2$), bis(diphenylphosphino)ferrocene (dppf), and urotropine in *N,N*-dimethylacetamide (DMA), the corresponding 2-benzazepines **144** and **145** were isolated as the only products albeit in moderate yields (Scheme 35). It should be noted here that cyclization of **142** gave a slightly higher isolated yield than **143**.

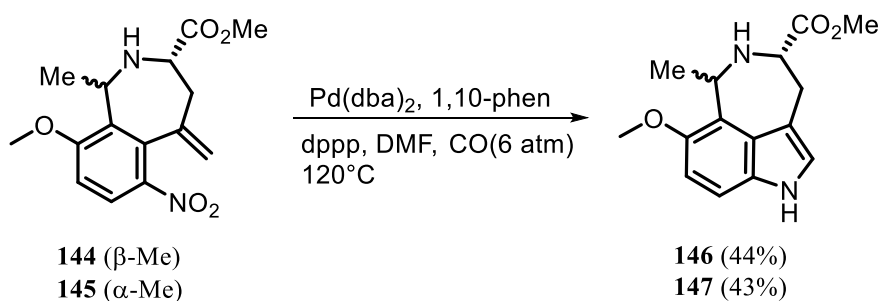
Scheme 35: Synthesis of 2-Benzazepines 144 and 145.



Watanabe-Cenini-Söderberg reductive *N*-heterocyclization of **144** and **145** using a

bis(dibenzylideneacetone)palladium-1,3-bis(diphenyl)phosphinopropane- 1,10-phenanthroline catalyst system in the presence of carbon monoxide ($p_{\text{CO}}=6$ atm, 120 °C) in *N,N*-dimethylformamide, furnished the azepino[5,4,3-*cd*]indoles **146** and **147** in 44% and 43% yield (Scheme 36), respectively.

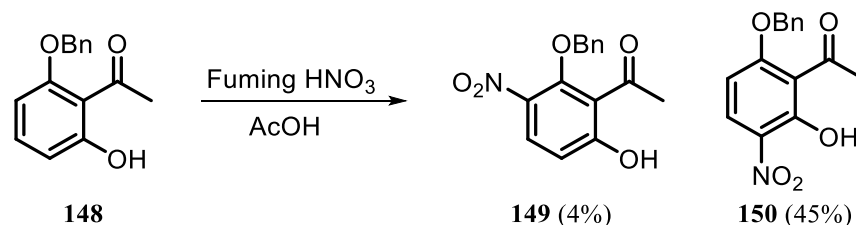
Scheme 36: *N*-heterocyclization to Give Azepinoindoles **146 and **147**.**



Finally, removal of the protecting groups in **146** and **147** would give hyrtioreticulins C & D. Demethylation using BBr_3 in DCM has been reported to be successful in similar substrates in the total synthesis of hyrtiazepine by Ito *et al.*⁴⁵ Treatment of **146** and **147** with BBr_3 under reported and varied temperature and solvent conditions did not furnish hyrtioreticulins; instead intractable mixtures were obtained in all attempted reactions. This prompted us to think about alternative protecting groups to replace the methoxy group. We anticipated that benzyl protecting group would be a better choice as it could be easily removed by reduction over Pd/C.^{43d,45}

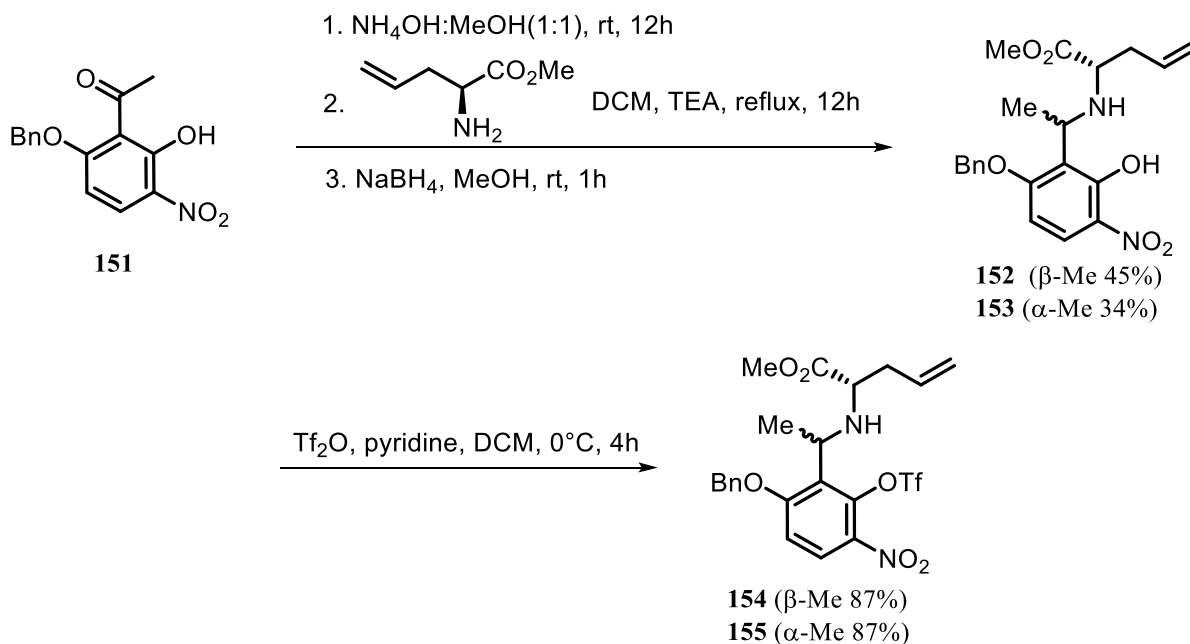
Thus, the synthesis was attempted again starting from nitration of 2-hydroxy-6-benzylacetophenone according to Cushman *et al.*⁶² which gave two products **149** and **150** in 4% and 45% yield respectively (Scheme 37).

Scheme 37: Nitration of 2-Hydroxy-6-benzylacetophenone



Imination trans-imination of the desired **150** with allylglycine methyl ester under the same conditions described above afforded the cis and trans products **153** and **152** which were readily separated by chromatography with 34% and 45% yields respectively. Treatment of **152** and **153** with triflic anhydride in presence of pyridine afforded the corresponding triflates **145** and **155** in excellent yields (Scheme 38).

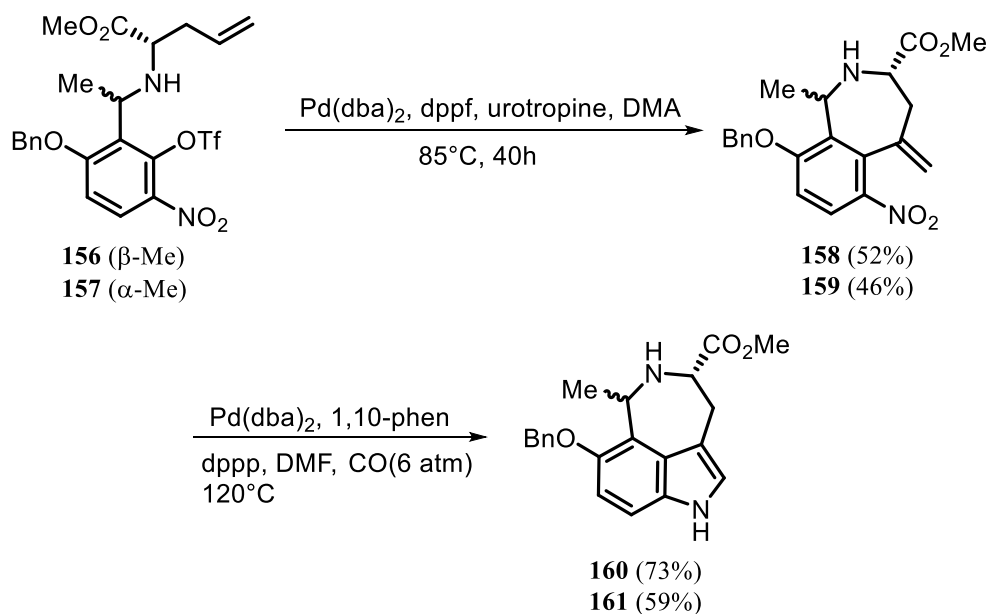
Scheme 38: Imination, Trans-imination and Triflation to Give 154 and 155



With the triflates **154** and **155** in hand, intramolecular Mizoroki-Heck reaction under Zhou's conditions provided 2-benzazepines **158** and **159** smoothly as expected. Watanabe-

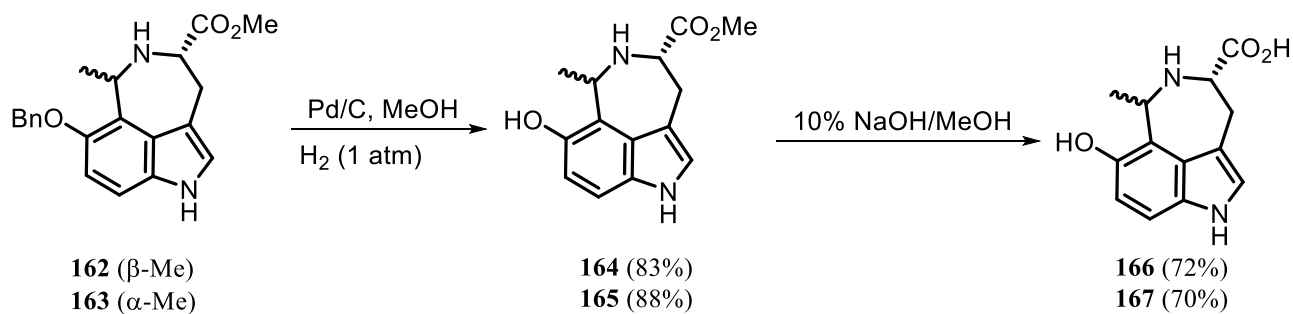
Cenini-Söderberg reductive *N*-heterocyclization of the nitroaromatic compounds **158** and **159** afforded the benzyl protected analogs of azepinoindoles **160** and **161** in 73% and 59% respectively (Scheme 39).

Scheme 39: Intramolecular Heck Reaction and Reductive *N*-heterocyclization



Finally, reduction of azepinoindoles **160** and **161** using Pd/C at 1 atm H_2 removed the benzyl group as expected to give hyrtioreticulins methyl esters **164** and **165** (Scheme 40). These compounds have previously been hydrolyzed using 10% NaOH/ H_2O in methanol to afford hyrtioreticulins C & D.^{43c}

Scheme 40: Synthesis of Hyrtioreticulins C & D



3.4 Conclusions

A concise linear total syntheses of the naturally occurring azepino[5,4,3-*cd*]indole diastereomers, hyrtioreticulins C & D has been completed. An imination, trans-imination, a regio-selective intramolecular Mizoroki-Heck reaction and a Watanabe-Cenini- Söderberg reductive *N*-heterocyclization are the key steps in the syntheses.

Chapter 4

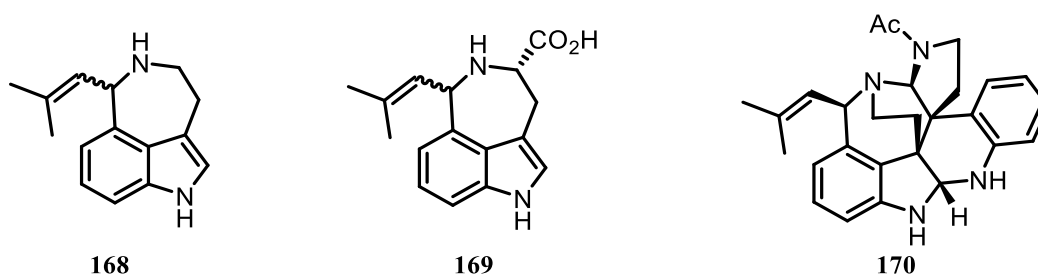
Attempted Synthesis of Aurantioclavine

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4.1 Introduction to Aurantioclavine

Aurantioclavine **168** was first isolated from the fungus *Penicillium aurantiovirens* in 1981 by Kozlovskii and coworkers.²⁷ This molecule and a related alkaloid, clavicipitic acid **169** isolated from the fungus *Claviceps fusiformis*, are proposed to be biosynthetic intermediates of the complex polycyclic alkaloids of the communesin family (Figure 8).⁶⁴ Members of this family display notable bioactivities, including insecticidal properties and cytotoxicity toward leukemia cell lines.

Figure 8: Structural Relationship of Aurantioclavine with Communesins 170



4.2 Notable Syntheses of Aurantioclavine

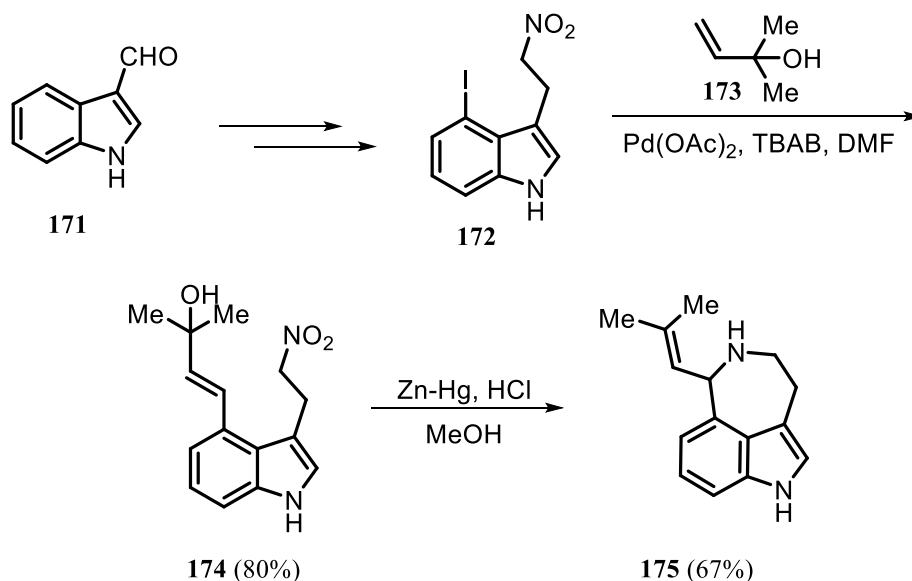
After the first total synthesis of aurantioclavine **168** in 1985 by Somei *et al.*,^{34a} several racemic and enantioselective syntheses have been reported to date.^{34,35,49} Stoltz and coworkers⁴⁸ reported the first enantioselective synthesis and determination of the absolute stereochemistry.

4.2.1 First Synthesis of Aurantioclavine by Somei

Somei and coworkers reported the first total synthesis of aurantioclavine (Scheme 41).^{34a} The starting 3-formylindole **171** was readily converted into nitroethylindole **172**. An intermolecular Heck reaction of 4-iodoindole **172** with allylic alcohol **173** provided **174**. Finally,

an intramolecular reductive amination using Zn-Hg/HCl afforded racemic aurantioclavine **175** (Scheme 41).

Scheme 41: Somei's Synthesis of Aurantioclavine

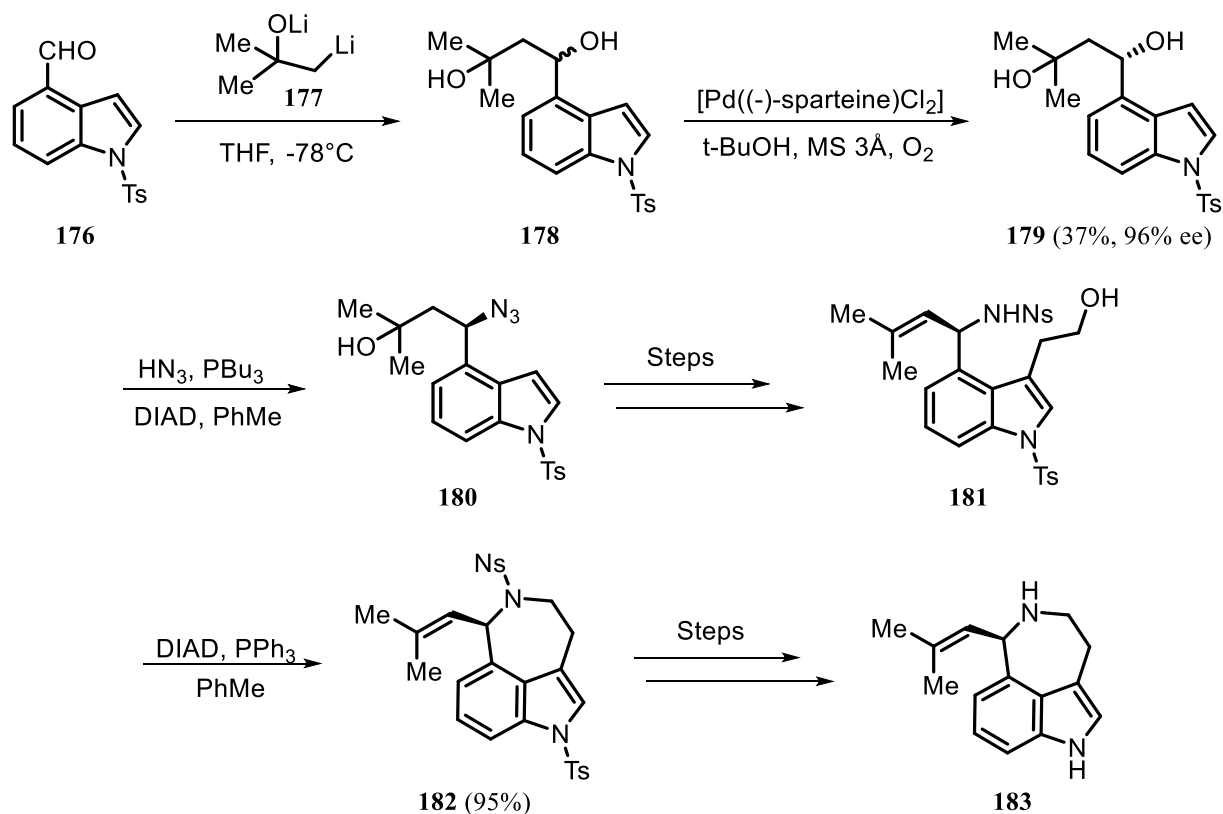


4.2.2 First Enantioselective Synthesis by Stoltz

Stoltz and coworkers⁴⁸ reported the first enantioselective synthesis of (-)-aurantioclavine (Scheme 42). The key reactions were a palladium-catalyzed oxidative kinetic resolution⁶⁵ and an intramolecular Mitsunobu reaction to install the azepine ring.

The starting 4-formylindole **176** was readily converted into racemic diol **178** by the addition of organolithium **177**. A palladium-catalyzed oxidative kinetic resolution in presence of chiral ligand (-)-sparteine gave **179** with 96% ee albeit in low isolated yield. The diol **179** was converted to **181** over five steps which underwent intramolecular Mitsunobu reaction to afford azepinoindole **182** in excellent yield, which after deprotection of tosyl and nosyl groups gave (-)-aurantioclavine. Absolute configuration of (-)-aurantioclavine was confirmed by X-ray analysis.

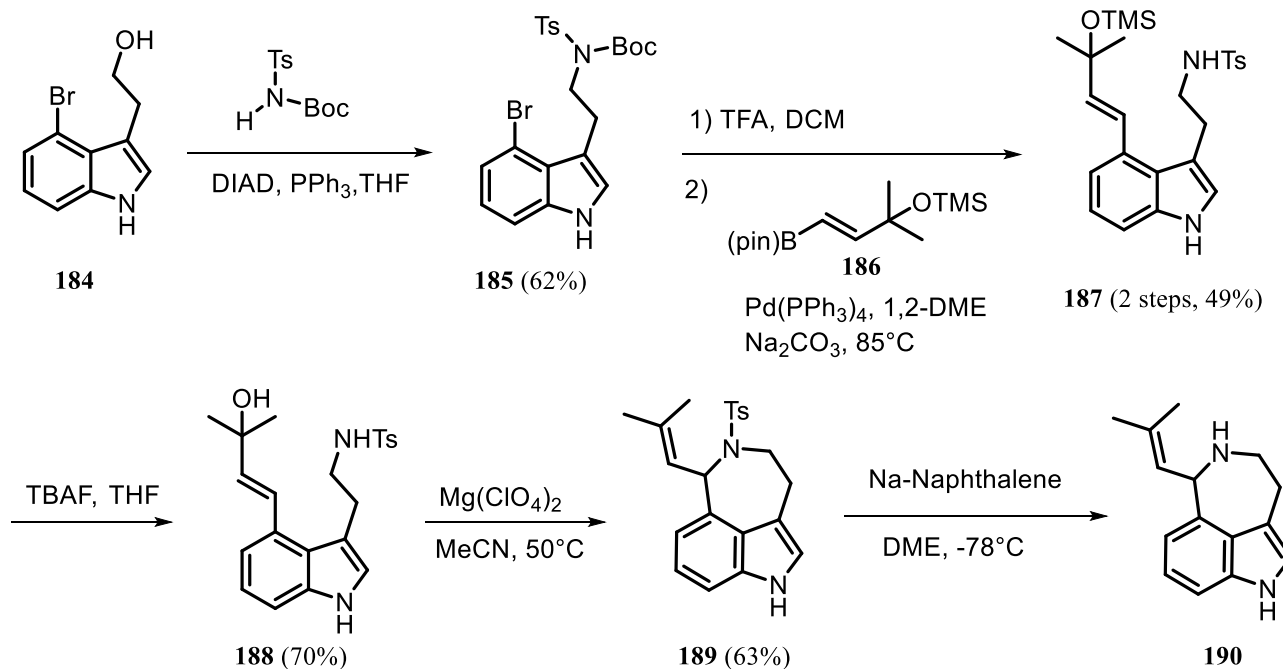
Scheme 42: Stoltz Synthesis of Aurantioclavine



4.2.3 Most recent Synthesis by Takemoto

The most recent scalable synthesis of aurantioclavine was reported by Takemoto and coworkers (Scheme 43).⁶⁶ The hydroxyethylindole **184** was converted to **185** using a Mitsunobu reaction. Removal of Boc group followed by a Suzuki-Miyaura coupling with boronic ester **186** introduced the allylic alcohol unit at the C-4 position. A desilylation using TBAF to afford **188**, and a Mg(ClO₄)₂ mediated allylic amination of **188** provided the *N*-tosylated azepinoindole **189**, which after removal of the tosyl group gave aurantioclavine **190**.

Scheme 43: Concise and Scalable Synthesis by Takemoto



4.3 Attempted Synthesis of Aurantioclavine

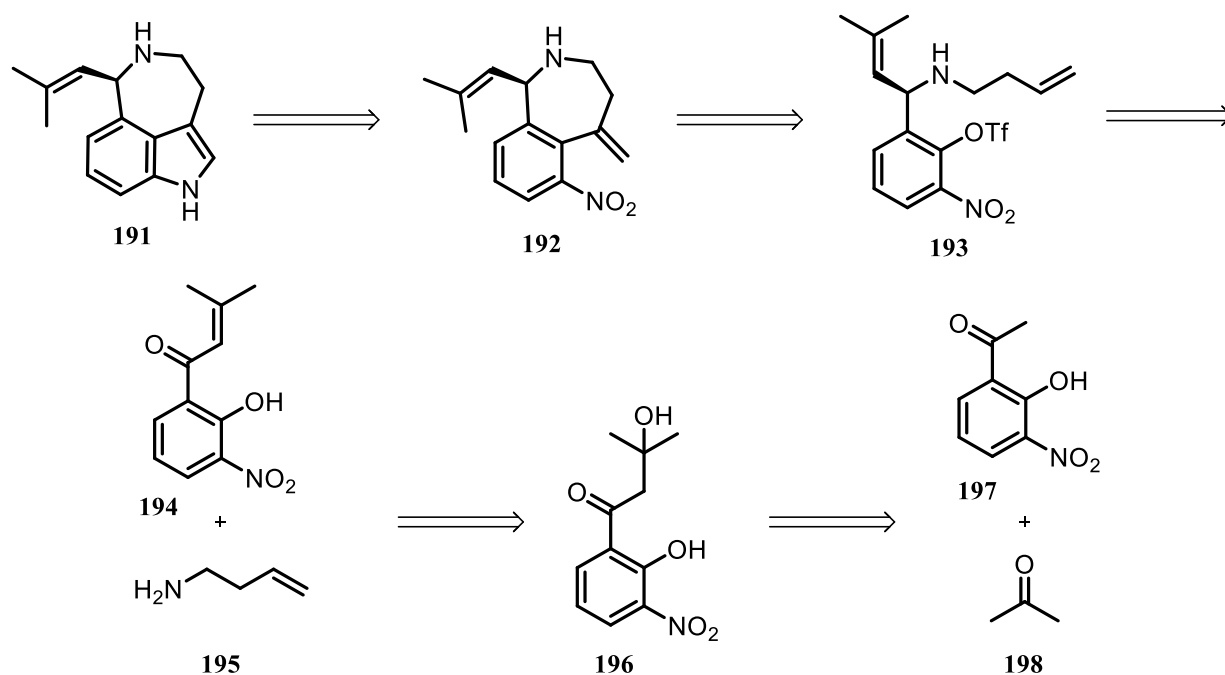
Our comparatively short strategy to synthesize azepinoindoles comprised of three important steps: reductive amination, intramolecular Mizoroki-Heck reaction, and Watanabe-Cenini-Söderberg reductive *N*-heterocyclization. Since aurantioclavine shares a common azepinoindole framework like fargesine and hyrtioreticulins, we anticipated that similar strategy could be used for its synthesis.

4.3.1 Retrosynthetic Analysis

The resemblance of aurantioclavine with the natural products previously synthesized in our lab prompted us to propose a relatively similar synthetic route (Scheme 44). Aurantioclavine possesses a 2-methylpropene substituent at the C-6 position of the ring. Therefore, our synthetic strategy was focused primarily on synthesizing a cyclization precursor having pre-installed 2-

methylpropene substituent. It was envisioned that aurantioclavine **191** could result from Watanabe-Cenini -Söderberg reductive *N*-heterocyclization of nitroaromatic **192**. Intramolecular Mizoroki-Heck reaction of **193** would give the desired reductive *N*-heterocyclization precursor **192**. The terminal alkene **193** could be prepared by reductive amination of enone derivative **194** and known 4-amino-1-butene **195**. The enone **194** could be obtained by dehydration of aldol adduct **196** which, in turn, could result from a crossed-aldol reaction between known 2-hydroxy-3-nitroacetophenone **197** and acetone **198**.

Scheme 44: Proposed Retrosynthetic Outline of Aurantioclavine

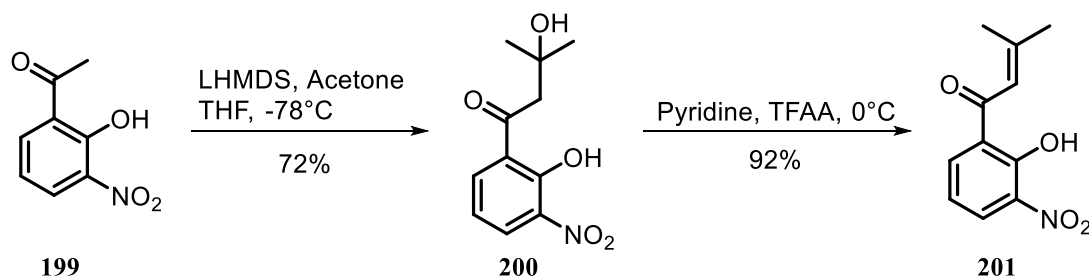


4.3.2 Results and Discussion

The synthesis of aurantioclavine began with the crossed aldol reaction between 2-hydroxy-3-nitroacetophenone **199** and acetone using LHMDS as a base at -78°C which furnished the expected aldol product **200** in 72% isolated yield. Dehydration of compound **200** in

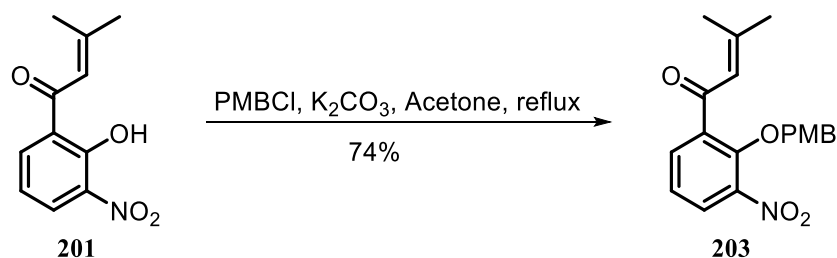
the presence of TFAA and pyridine at 0 °C went smoothly to afford the enone **201** in excellent yield (Scheme 45).

Scheme 45: Aldol Reaction and Dehydration of the Aldol Product



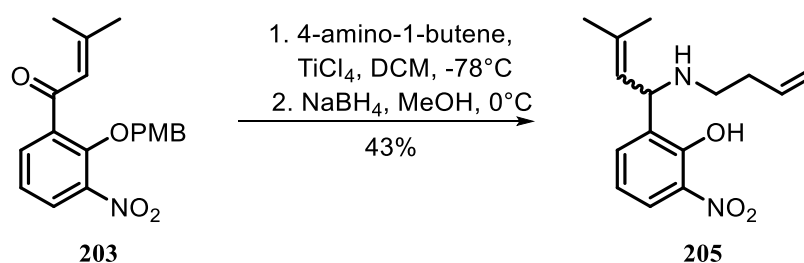
Attempts of reductive amination of **201** with 4-amino-1-butene under various conditions yielded only the undesired retro-aldol product. With a view that dehydration step could be performed after reductive amination, some reductive amination protocols found in the literature were also tried with the ketone **200**. Unfortunately, formation of retro-aldol products was even more pronounced in reactions when **200** was used in reactions. Additionally, attempts to protect the phenolic group of **201** with triflic anhydride and pyridine were also unsuccessful. Therefore, the hydroxy group of **201** was protected using *p*-methoxybenzyl chloride (PMBCl) to give **203** in good yield (Scheme 46).

Scheme 46: Protection of Phenol Using PMBCl



The PMB-protected ketone **203** finally underwent TiCl₄-mediated reductive amination with 4-amino-1-butene at -78 °C in the presence of sodium borohydride as reducing agent to give the desired amine **205**, albeit without the protecting group (Scheme 47). This unexpected removal of *p*-methoxybenzyl group during the reductive amination procedure was beneficial in the sense that it could save the deprotection step.

Scheme 47: Reductive Amination of Enone **203**



The terminal alkene **205**, after converting the hydroxy group into triflate, would undergo intramolecular Mizoroki-Heck reaction as evidenced by our previous syntheses (*vide supra*). Attempts to convert **205** into a triflate as cyclization precursor using triflic anhydride and pyridine at varying temperature conditions were unsuccessful as all our endeavors resulted in decomposed products.

4.3.3 Conclusions

A short synthesis of aurantioclavine is currently underway. A crossed-aldol reaction and a TiCl₄-mediated reductive amination served as an expedient route to the Heck reaction precursor **205**. Further optimization is deemed necessary to perform the Heck reaction, which would, in turn, lead to the azepinoindole alkaloid aurantioclavine.

Overall Conclusion

Short synthetic schemes leading to naturally occurring azepino[5,4,3-*cd*]indole alkaloids cimitrypazepine, fargesine and diastereomeric hyrtioreticulins C & D have been developed. A terminal alkene-tethered tetra-substituted nitrobenzene analogue served as a key intermediate for a sequential formation for the azepine ring and the pyrrole ring of the natural products.

The intramolecular Mizoroki-Heck reaction using one of the standard catalyst systems, palladium diacetate – tri(*o*-tolyl)phosphine – triethyl amine (125 °C) provided, in addition to the desired seven-membered ring, the eight-membered rings as minor products. Alternatively, intramolecular cyclization of related substrates using bis(dibenzylideneacetone)palladium (Pd(dba)₂), bis(diphenylphosphino)ferrocene (dppf), and urotropin in *N,N*-dimethylacetamide (DMA) provided a seven membered rings as the single product. Thus, our results suggested that the synthesis of both 1,1-disubstituted and 1,2-disubstituted alkenes can be obtained from the same substrate simply by modifying the catalyst system.

The Watanabe-Cenini-Söderberg reductive *N*-heterocyclization served as an efficient late stage cyclization protocol for the syntheses of above mentioned azepinoindole alkaloids. The catalyst system Pd(dba)₂-dppp-1,10-phenanthroline using DMF as solvent at 120 °C under 6 atm of carbon monoxide was successfully utilized in all of the four syntheses to afford the desired indole ring, which further elaborated its synthetic utility for the synthesis of a variety of functionalized indoles.

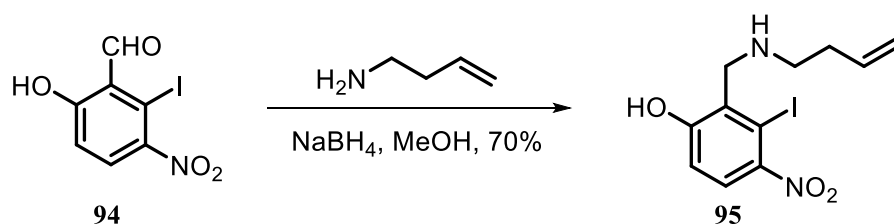
Chapter 5

Supporting Information: Experimental Procedures

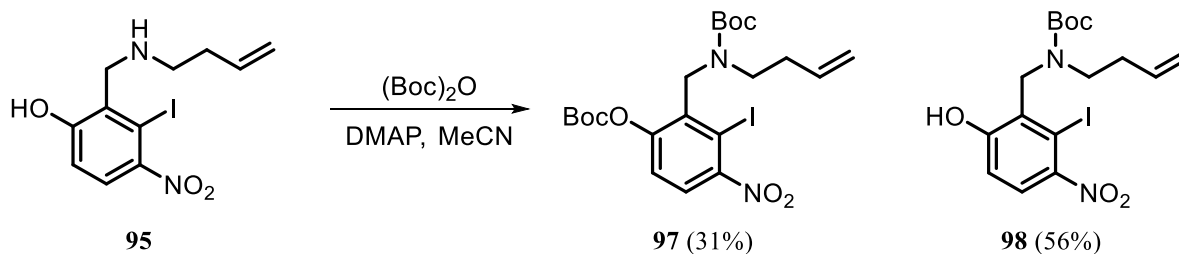
5.1 Supporting Information for Chapter 2: Cimitrypazepine and Fargesine	53
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General Procedures. NMR spectra were determined in CDCl₃ at 600 MHz (¹H NMR) and 150 MHz (¹³C NMR), 400 MHz (¹H NMR) and 100 MHz (¹³C NMR), or at 270 MHz (¹H NMR) and 67.5 MHz (¹³C NMR). The chemical shifts are expressed in δ+ values relative to SiMe₄ (0.0 ppm, ¹H and ¹³C) or CDCl₃ (77.0 ppm, ¹³C) internal standards. ¹H-¹H coupling constants are reported as calculated from spectra, thus a slight difference between *J*_{a,b} and *J*_{b,a} is usually observed. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Hexanes and ethyl acetate were distilled from calcium hydride. Anhydrous acetonitrile, benzene, dichloromethane, 1,4-dioxane, *N,N*-dimethylformamide, and toluene were used as received. Chemicals prepared according to literature procedures have been footnoted the first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in oven-dried glassware. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure unless otherwise stated. Chromatography was performed on silica gel 60 (40-63 μm, Sorbtech). Melting points (uncorrected) were recorded directly from products obtained by chromatography.

5.1 Supporting Information for Chapter 2: Cimitrypazepine and Fargesine



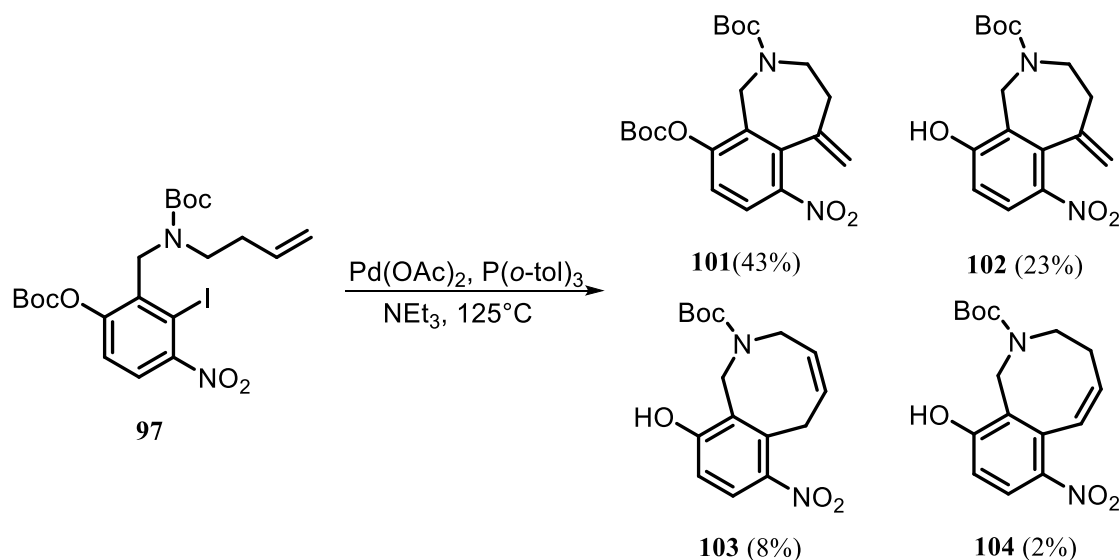
To a stirred solution of 6-hydroxy-2-iodo-3-nitrobenzaldehyde (**94**), (200 mg, 0.682 mmol) and 4-amino-1-butene (48.5 mg, 0.682 mmol) in methanol (2.1 mL) at ambient temperature was added NaBH₄ (51.6 mg, 1.36 mmol). The mixture was stirred at ambient temperature for 1 h. Water (21 mL) was added and the resulting mixture was extracted with EtOAc (3×25 mL). The combined organic layers were dried (MgSO₄), filtered and solvents were removed under reduced pressure. The crude product was purified by chromatography (CHCl₃/MeOH/NH₄OH, 100:10:1) affording **95** (166 mg, 0.477 mmol, 70%) as a yellow solid. Analytical data for **95**: mp= 158-160 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J*= 8.4 Hz, 1H), 7.0 (br s, 2H) 6.80 (d, *J*= 9.2 Hz, 1H), 5.77 (ddt, *J*= 17.6, 10.4, 6.4, Hz, 1H), 5.17 (d, *J*= 18.0 Hz, 1H), 5.16 (d, *J*= 9.2 Hz, 1H), 4.32 (s, 2H), 2.79 (t, *J*= 6.8 Hz, 2H), 2.35 (q, *J*= 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 162.7, 146.3, 134.6, 126.1, 125.5, 118.2, 116.8, 92.8, 58.5, 47.2, 33.2; IR (ATR) 2954, 2874, 2174, 1524, 1453, 1338, 1243, 829, 727 cm⁻¹; HRMS (ESI) calcd for C₁₁H₁₄IN₂O₃ (M+H⁺) 249.0049, found 249.0049.



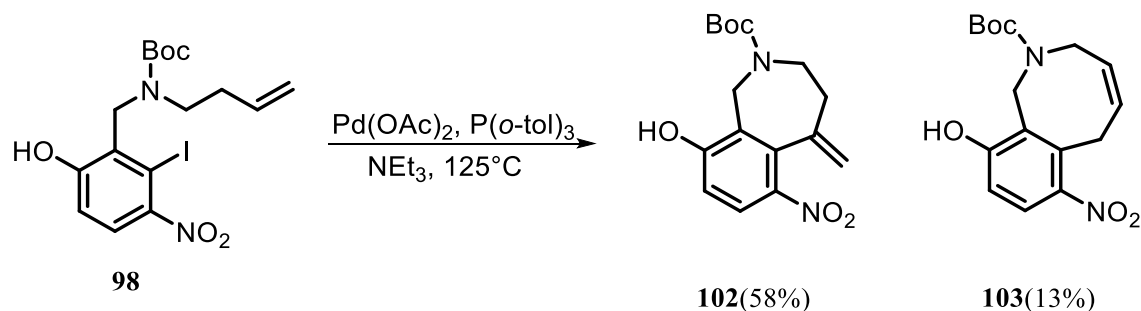
To a stirred solution of compound **95** (166 mg, 0.477 mmol) in acetonitrile (MeCN, 4.8 mL) was added di-*t*-butyldicarbonate ((Boc)₂O, 208 mg, 0.954 mmol) and 4-(*N,N*-dimethylamino)pyridine (DMAP, 11.8 mg, 0.095 mmol) at ambient temperature. The mixture was stirred for 18 h. The solvent was removed under reduced pressure and the crude product was dissolved in water (20 mL). The mixture was extracted with EtOAc (3×20 mL). The combined organic layers were dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 98:2) to give, in order of elution, **97** (82 mg, 0.150 mmol, 31%) as a pale-yellow oil and **98** (119 mg, 0.265 mmol, 56%) as a pale yellow solid. Analytical data for **97**: ¹H NMR (400 MHz, CDCl₃, 50 °C) δ 7.58 (d, *J*= 9.2 Hz, 1H), 7.29 (d, *J*= 9.2 Hz, 1H), 5.77 (ddt, *J*= 17.2, 10.0, 6.8, Hz, 1H), 5.01 (d, *J*= 18.8 Hz, 1H), 4.97 (d, *J*= 10.0 Hz, 1H), 4.75 (s, 2H), 3.06 (br s, 2H), 2.22 (q, *J*= 7.2 Hz, 2H), 1.56 (s, 9H), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃, 60 °C, mixture of rotamers) δ 155.1, 153.5, 151.9, 150.6, 135.9, 135.3, 124.1, 123.4, 116.6, 93.4, 85.1, 80.1, 50.5, 45.7, 32.7, 28.7, 28.5, 28.3, 27.9, 27.7; IR (ATR) 3082, 2978, 2936, 1760, 1693, 1123 cm⁻¹; HRMS (ESI) calcd for C₂₁H₃₀IN₂O₇ (M+H⁺) 549.1098, found 549.1104.

Analytical data for **98**: mp=105-106 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, *J*= 9.2 Hz, 1H), 6.93 (d, *J*= 8.8 Hz, 1H), 5.75 (ddt, *J*= 17.2, 10.0, 6.8, Hz, 1H), 5.07-5.01 (m, 2H), 4.82 (s, 2H), 3.42 (t, *J*= 7.2 Hz, 2H), 2.34 (pent, *J*= 7.6 Hz, 2H), 1.50 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 160.7, 159.2, 147.6, 134.6, 128.2, 127.4, 118.1, 117.6, 95.7, 83.0, 51.5, 46.5, 32.9, 28.5; IR

(ATR) 3078, 2980, 2937, 1737, 1641, 1525, 1442 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{22}\text{IN}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 449.0573, found 449.0578.



A solution of **97** (749 mg, 1.37 mmol), $\text{Pd}(\text{OAc})_2$ (15.3 mg, 0.068 mmol), and tri(*o*-tolyl)phosphine (TTP, 41.4 mg, 0.136 mmol) in triethylamine (TEA, 6.8 mL) was heated at 125°C (2 h). After 2 h, the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (10 mL) and filtered (Celite). The filtrate was evaporated to remove the solvents. Purification of the crude product by chromatography (hexanes/EtOAc, 98:2 then 8:2) gave, in order of elution, **101** (250 mg, 0.595 mmol, 43%) as pale yellow oil, compound **103** (10 mg, 0.031 mmol, 2%) as pale yellow solid, **104** (36 mg, 0.112 mmol, 8%) as yellow oil, and **102** (102 mg, 0.318 mmol, 23%) as yellow solid.



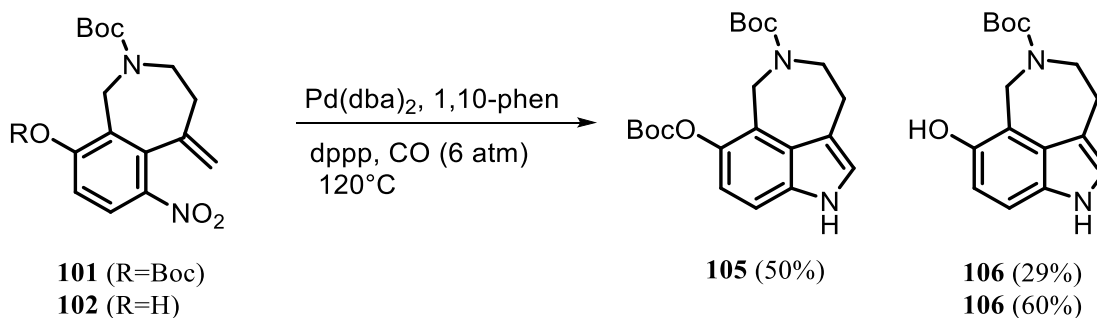
A solution of **98** (132 mg, 0.295 mmol), palladium diacetate ($\text{Pd}(\text{OAc})_2$, 3.3 mg, 0.015 mmol), and tri(*o*-tolyl)phosphine (TTP, 9.0 mg, 0.030 mmol) in triethylamine (TEA, 1.5 mL) was heated at 125 °C for 6 h. The reaction mixture was cooled to ambient temperature, diluted with EtOAc (10 mL) and filtered (Celite). The solvent was removed under reduced pressure from the filtrate. Purification of the crude product by chromatography (hexanes/EtOAc, 95:5 then 90:10) gave, in order of elution, **103** (12 mg, 0.037 mmol, 13%) as yellow oil and compound **102** (55 mg, 0.172 mmol, 58%) as yellow solid.

Analytical data for **101**: ^1H NMR (600 MHz, CDCl_3 , -52 °C, mixture of rotamers) δ 7.73 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.26 (d, J = 8.9 Hz, 1H), 7.23 (d, J = 8.9 Hz, 1H), 5.27 (s, 2H), 4.98 (s, 1H), 4.97 (s, 1H), 4.47 (br s, 2H), 4.21 (br s, 2H) 3.25 (br s, 2H), 3.10 (br s, 2H), 2.60 (br s 2H), 2.52 (br s, 2H), 1.60 (s, 9H), 1.58 (s, 9H), 1.44 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3 , -52 °C, mixture of rotamers) δ 154.2, 154.0, 151.1, 150.9, 149.7, 149.2, 146.9, 146.7, 143.4, 143.2, 139.9, 139.4, 131.2, 123.6, 123.2, 122.3, 121.1, 116.9, 116.8, 84.6, 80.5, 79.9, 50.1, 49.9, 44.4, 44.0, 36.3, 35.6, 28.1, 28.0, 27.4, 27.3; IR (ATR) 2981, 2936, 2359, 1760, 1694, 1228, 1132 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{22}\text{IN}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 421.1975, found 421.1977.

Analytical data for **102**: mp= 137-138 °C; ^1H NMR (400 MHz, CDCl_3 , 45 °C) δ 7.62 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 5.32 (s, 1H), 5.10 (s, 1H), 4.31 (br s, 2H), 3.77 (br s, 2H), 2.50 (t, J = 5.6 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3 , 45 °C) δ 158.2, 156.7, 143.2, 142.0, 140.1, 124.9, 124.7, 81.7, 51.1, 44.6, 37.0, 28.3; IR (ATR) 3221, 2981, 2933, 1695, 1652, 1577, 1520, 1457, 1423, 1307 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 321.1450, found 321.1451.

Analytical data for **103**: ^1H NMR (600 MHz, CDCl_3) δ 10.40 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 6.36 (dt, J = 10.1, 8.4 Hz, 1H), 5.83 (dt, J = 10.1, 7.2 Hz, 1H), 4.69 (s, 2H), 4.14 (d, J = 7.2 Hz, 2H), 3.74 (d, J = 7.8 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 161.3, 157.6, 142.7, 138.8, 136.6, 127.5, 126.5, 125.4, 117.5, 82.3, 46.7, 46.2, 29.4, 28.5; IR (ATR) 3099, 2978, 2934, 1711, 1641, 1519, 1423, 1264 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 321.1450, found 321.1446.

Analytical data for **104**: mp 154-155 $^\circ\text{C}$; ^1H NMR (600 MHz, CDCl_3) δ 11.52 (s, 1H), 8.10 (d, J = 9.6 Hz, 1H), 7.03 (d, J = 10.8 Hz, 1H), 6.96 (d, J = 9.6 Hz, 1H), 6.14 (dt, J = 11.4, 8.4 Hz, 1H), 4.89 (br s, 1H), 4.09 (br s, 1H), 3.76 (br s, 1H), 2.71 (br s, 1H), 2.47 (br s, 1H), 1.81 (br s, 1H), 1.49 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 162.7, 158.2, 140.1, 134.6, 131.4, 128.5, 127.6, 124.4, 117.3, 82.9, 43.9, 41.4, 28.6, 28.4; IR (ATR) 2980, 2934, 2871, 2720, 2632, 1641, 1520, 1449 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 321.1450, found 321.1446.



A solution of **101** (102 mg, 0.243 mmol), bi(dibenzylidenacetone)palladium (13.9 mg, 0.024 mmol), 1,3-bis(diphenylphosphino)propane (10 mg, 0.024 mmol), and 1,10-phenanthroline (8.7 mg, 0.048 mmol) in anhydrous *N,N*-dimethylformamide (1.3 mL), in an ACE-Glass pressure tube fitted with a pressure head, was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120°C for 20 h. The mixture was cooled to ambient temperature, diluted with EtOAc (5 mL), and washed with

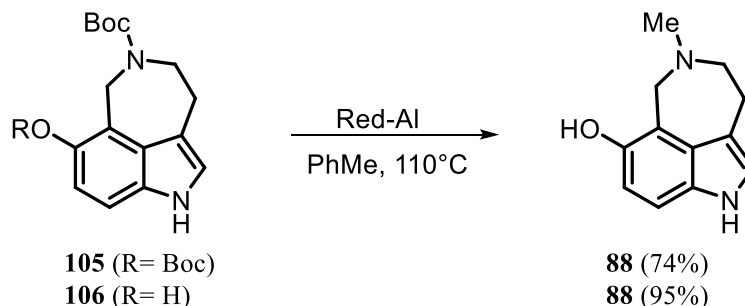
brine (3×5 mL). The organic phase was dried (MgSO₄) and filtered. The solvent was removed under reduced pressure and the resulting residue was purified by chromatography (hexanes/EtOAc, 9:1 then 4:1) to afford, in order of elution, **105** (47 mg, 0.12 mmol, 50%) as a pale yellow solid and **106** (20 mg, 0.069 mmol, 29%) as a pale yellow solid.

A solution of **102** (48.0 mg, 0.150 mmol), bis(dibenzylideneacetone)-palladium (6.0 mg, 0.010 mmol), 1,3- bis(diphenylphosphino)propane (4.3 mg, 0.010 mmol), and 1,10-phenanthroline (3.8 mg, 0.021 mmol) in anhydrous *N,N*-dimethylformamide (0.6 mL), in an ACE-Glass pressure tube fitted with a pressure head, was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120 °C for 72 h. The mixture was cooled to ambient temperature, diluted with EtOAc (3 mL), and washed with brine (3×3 mL). The organic phase was dried (MgSO₄) and filtered. The solvent was removed under reduced pressure and the resulting residue was purified by chromatography (hexanes/EtOAc, 4:1) to afford **106** (26 mg, 0.09 mmol, 60%) as a pale yellow solid.

Analytical data for **105** from a mixture of rotamers: mp= 153–155 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.20 (br s, 1H), 7.16 (d, *J*= 8.8 Hz, 0.5H), 7.15 (d, *J*= 9.2 Hz, 0.5H), 6.97 (s, 1H), 6.90 (d, *J*= 8.8 Hz, 1H), 4.90 (s, 1H), 4.82 (s, 1H), 3.76 (t, *J*= 6.0 Hz, 1H), 3.71 (t, *J*= 4.8, 1H), 3.14 (t, *J*= 5.6 Hz, 1H), 3.10 (t, *J*= 4.8 Hz, 1H), 1.58 (s, 4.5H), 1.55 (s, 4.5H), 1.46 (s, 4.5H), 1.39 (s, 4.5H); ¹³C NMR (100 MHz, CDCl₃) δ 155.3, 155.0, 152.9, 152.8, 140.9, 140.5, 135.0, 134.8, 125.9, 125.8, 124.4, 124.2, 122.8, 122.6, 116.4, 116.3, 115.5, 115.2, 110.1, 109.9, 83.2, 83.2, 80.0, 79.8, 49.1, 48.3, 47.8, 28.8, 28.6, 28.0, 27.9, 27.7, 26.6; IR (ATR) 3315, 2978, 2935, 1752, 1693, 1669, 1140 cm⁻¹; HRMS (ESI) calcd for C₂₁H₂₉N₂O₅ (M+H⁺) 389.2076, found 389.2078.

Analytical data for **106**: mp= 186-188 °C; ¹H NMR (400 MHz, CDCl₃, 60°C) δ 7.82 (br s, 1H), 7.06 (d, *J*= 8.4 Hz, 1H), 6.96 (s, 1H), 6.68 (d, *J*= 8.4 Hz, 1H), 4.93 (s, 2H), 3.77 (br s, 2H), 3.14

(br s, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers) δ 155.0, 146.0, 145.7, 131.8, 126.1, 125.9, 122.2, 122.0, 116.9, 113.8, 113.4, 112.0, 111.6, 109.4, 79.2, 79.1, 49.0, 48.9, 48.4, 48.0, 40.4, 40.2, 40.0, 39.8, 39.6, 28.5, 28.4, 27.5, 26.7; IR (ATR) 3335, 2972, 1665, 1582, 1367, 1165 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 289.1552, found 289.1552.

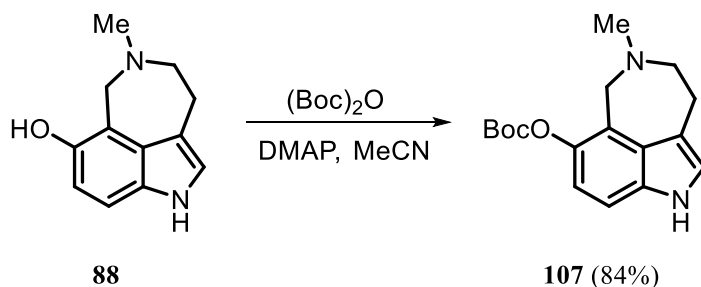


To a solution of **105** (110 mg, 0.283 mmol) in anhydrous toluene (28 mL) under a nitrogen atmosphere was added sodium bis(2-methoxyethoxy)aluminumhydride (in toluene ~3.5 M, 1.9 mL, 6.65 mmol) drop wise. The mixture was stirred at 110 °C for 3 h and then allowed to cool to ambient temperature. Brine (56 mL) was added, and the mixture was extracted with EtOAc (3×60 mL). The organic phases were combined, dried (MgSO_4), and filtered. The solvent was removed under reduced pressure and the residue was purified by chromatography (EtOAc/MeOH, 9:1) to give **88** (42 mg, 0.21 mmol, 74%) as yellow paste.

To a solution of **106** (218 mg, 0.756 mmol) in a mixture of toluene (70 mL) and tetrahydrofuran (5 mL) under a nitrogen atmosphere was added sodium bis(2-methoxyethoxy)aluminumhydride (in toluene ~3.5 M, 5.07 mL, 17.7 mmol) drop wise. The mixture was stirred at 110 °C for 4 h and then allowed to cool to ambient temperature. Brine (150 mL) was added, and the mixture was extracted with EtOAc (3×150 mL). The organic phases were combined, dried (MgSO_4), and filtered. The solvent was removed under reduced

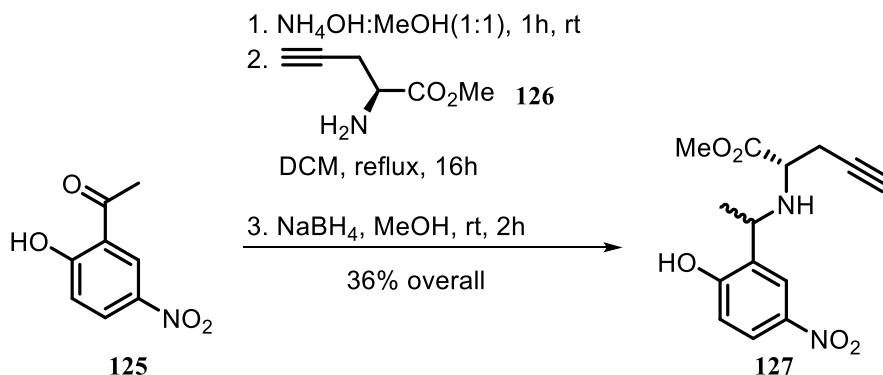
pressure and the resulting residue was purified by chromatography (EtOAc/MeOH, 9:1) to give **88** (145 mg, 0.717 mmol, 95%) as a yellow paste.

Analytical data for **88**: ^1H NMR (400 MHz, CD_3OD) δ 7.08 (d, J = 8.8 Hz, 1H), 7.00 (s, 1H), 6.67 (d, J = 8.8 Hz, 1H), 4.26 (s, 2H), 3.22 (t with further fine splittings, J = 5.2 Hz, 2H), 3.12 (t with further fine splittings, J = 5.6 Hz, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 148.9, 132.9, 127.0, 124.5, 113.4, 112.5, 110.9, 107.5, 60.6, 57.8, 44.9, 24.4; IR (ATR) 3284, 2913, 1704, 1583, 1437, 1363, 789 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$) 203.1184, found 203.1182.



To a stirred solution of **88** (20 mg, 0.099 mmol) in MeCN (1.0 mL) was added DMAP (1.3 mg, 0.010 mmol) at ambient temperature. The mixture was cooled to 0 °C and $(\text{Boc})_2\text{O}$ (23.7 mg, 0.108 mmol) as a solution of MeCN (0.5 mL) was added in portions. The resulting mixture was stirred at 0 °C for 6 h. The solvent was removed under reduced pressure and the crude product was purified by chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 20:1) to afford **107** (25 mg, 0.083 mmol, 84%) as yellow oil. ^1H NMR and ^{13}C NMR data were in accordance with literature value. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 303.1709, found 303.1708.

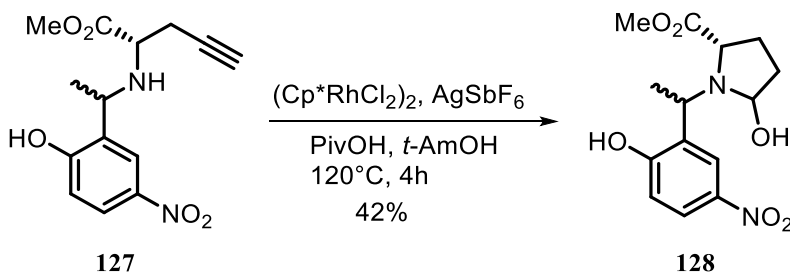
5.2 Supporting Information for Chapter 3: Hyrtioreticulins C & D



A solution of NH_4OH and MeOH (1:1, v/v) (1.7 mL) was added dropwise to 2-hydroxy-3-nitroacetophenone **126** (1.825 g, 10.07 mmol) at ambient temperature. The resulting mixture was stirred for 2 h and the solvents were removed under reduced pressure to obtain yellow solid. The crude imine was dissolved in dichloromethane (50 mL), and (S)-2-amino-4-pentynoic acid methyl ester hydrochloride (2.45 g, 14.95 mmol) and triethylamine (1.51 g, 14.95 mmol) were added. The mixture was stirred at ambient temperature for 21 h. Solvents were removed under reduced pressure and the crude product was dissolved in methanol (50 mL). To the stirred mixture at ambient temperature was added NaBH_4 (575 mg, 14.95 mmol) in one portion. The resulting mixture was stirred for 2 h at ambient temperature. The volatiles were removed under reduced pressure and the crude product was purified by chromatography ($\text{DCM}/\text{MeOH}/\text{NH}_4\text{OH}$, 100:2:1) to afford **127** as an inseparable mixture of diastereomers (1.041 g, 3.56 mmol, 36% overall) as yellow solid.

Analytical data for **127**: mp = 87-88 °C; ^1H NMR (400 MHz, CDCl_3) (as a mixture of diastereomers) δ 11.85 (br s, 1H) 11.75 (br s, 1H), 8.09 (t with further splitting, $J = 2.8$ Hz, 1H), 8.06 (t with further splitting, $J = 3.2$ Hz, 1H), 7.95 (d, $J = 2.8$ Hz, 1H), 7.88 (d, $J = 2.8$ Hz, 1H), 6.88 (d, $J = 9.2$ Hz, 1H), 6.87 (d, $J = 9.2$ Hz, 1H), 4.18 (q, $J = 6.8$ Hz, 1H), 3.99 (q, $J = 6.8$ Hz, 1H),

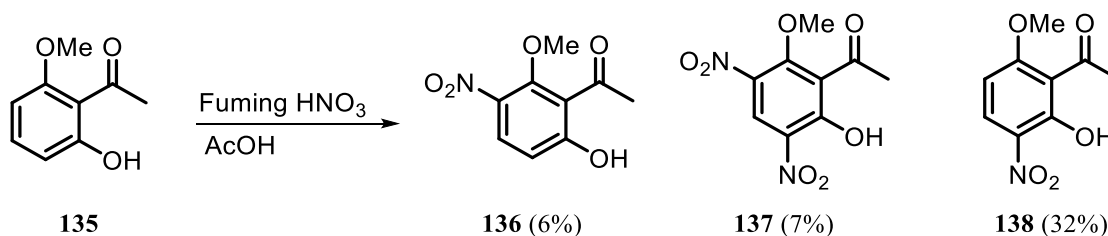
3.82 (s, 3H), 3.77 (s, 3H), 3.56 (m, 1H), 3.38 (m, 1H), 2.72 (m, 6H), 2.16 (t, J = 2.4 Hz, 1H), 2.12 (t, J = 2.4 Hz, 1H), 1.53 (d, J = 2.8 Hz, 3H), 1.52 (d, J = 3.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) (as a mixture of diastereomers) δ 172.3, 171.7, 163.7, 163.6, 140.6, 140.6, 126.5, 126.2, 125.5, 125.4, 125.0, 124.4, 117.8, 117.8, 77.8, 73.0, 72.8, 57.9, 57.9, 56.8, 55.5, 55.1, 55.0, 53.0, 29.9, 23.7, 22.7, 21.7, 21.3; IR (ATR) 3326, 2943, 2229, 2117, 1736, 1544, 1452, 1094, 925 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 293.1137, found 293.1131



In an ACE-Glass pressure tube, **127** (102 mg, 0.349 mmol), pivalic acid (178 mg, 1.745 mmol), *t*-amyl alcohol (3.6 mL), and pentamethylcyclopentadienylrhodium(III) chloride dimer ($[\text{Rh}(\text{C}_5\text{Me}_5)\text{Cl}_2]_2$) (5.4 mg, 0.009 mmol) were added respectively. To the stirred mixture was added silver hexafluoroantimonate $[\text{AgSbF}_6]$ (12.0 mg, 0.035 mmol) and the pressure tube was capped tightly. The resulting mixture was stirred at 120 °C for 4 h. The reaction mixture was cooled at ambient temperature and filtered through a pad of silica gel. Solvents were removed under reduced pressure from the filtrate and the crude product was purified by chromatography (MeOH/DCM, 4:96) to afford **128** (46 mg, 0.15 mmol, 43%) as a grey solid.

Analytical data for **128**: mp= 74-75 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.01 (dd, J = 9.2, 2.8 Hz, 2H), 7.97 (d, J = 2.8 Hz, 1H), 6.83 (d, J = 9.2 Hz, 1H), 5.41 (d, J = 3.6 Hz, 1H), 4.08 (q, J = 7.2 Hz, 1H), 3.76 (s, 3H), 3.54 (dd, J = 10.2, 6.0 Hz, 1H), 2.25 (m, 4H), 1.58 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.6, 159.1, 141.1, 124.4, 124.1, 123.7, 117.6, 88.2, 62.2, 52.5,

50.5, 30.9, 25.9, 24.6; IR (ATR) 3327, 2243, 2229, 2071, 1739, 1599, 1498, 1360, 1241, 1094, 925 cm⁻¹.



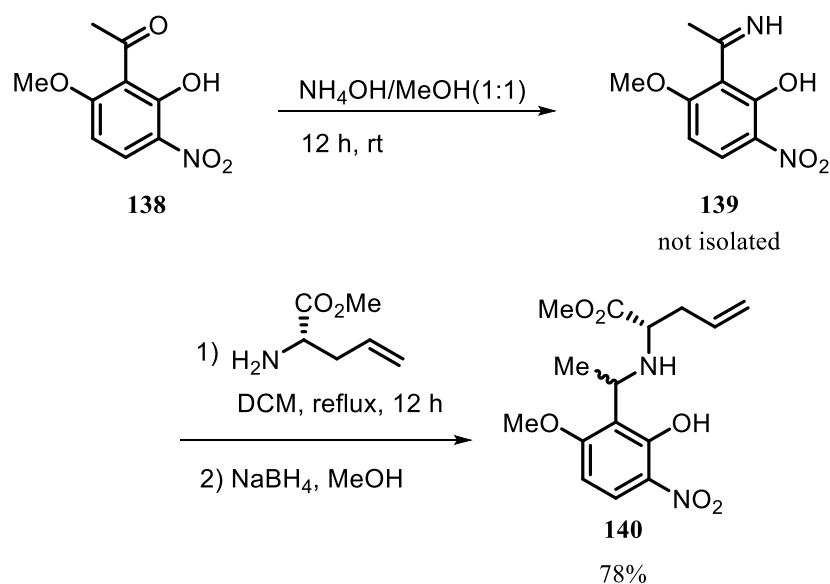
2-Hydroxy-6-methoxyacetophenone (3.32 g, 20.0 mmol) was dissolved in glacial acetic acid (20 mL) and fuming nitric acid (2.0 mL) was added dropwise. The reaction mixture was stirred in a round-bottomed flask equipped with a drying tube (CaCl₂) at room temperature for 40 min, and then at 50 °C for 18 h. The solvents were removed under reduced pressure, and water (80 mL) was added. The mixture was extracted with EtOAc (3×80 mL). The combined organic layers were dried (MgSO₄), filtered and solvents were removed under reduced pressure. The crude product was purified by chromatography (EtOAc/hexane, 2:8) affording, in the order of elution, **136** (321 mg, 1.23 mmol, 6%) as a yellow solid and **137** (369 mg, 1.44 mmol, 7%) as yellow solid and **138** (1.35 g, 6.40 mmol, 32%) as a yellow solid.

Analytical data for **136**: mp = 68-69 °C; ¹H NMR (400 MHz, CDCl₃) δ 13.32 (s, 1H), 8.06 (d, *J* = 9.6 Hz, 1H), 6.81 (d, *J* = 9.2 Hz, 1H), 3.97 (s, 3H), 2.78 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 204.7, 167.5, 157.9, 134.8, 132.5, 114.9, 114.1, 63.2, 32.4; IR (ATR) 3091, 2957, 1942, 1631, 1592, 1336, 1297, 1224, 1100, 791 cm⁻¹; HRMS (ESI) calcd for C₉H₁₀NO₅ (M+H⁺) 212.0559, found 212.0556.

Analytical data for **137**: mp = 70-71 °C; ¹H NMR (400 MHz, CDCl₃) δ 11.62 (s, 1H), 8.85 (s, 1H), 4.00 (s, 3H), 2.63 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 198.1, 157.7, 156.2, 135.2, 129.1,

126.5, 125.1, 64.4, 32.1; IR (ATR) 3210, 2958, 2155, 1790, 1713, 1587, 1530, 1125, 960, 665 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_9\text{H}_9\text{N}_2\text{O}_7$ ($\text{M}+\text{H}^+$) 257.0410, found 257.0398.

Analytical data for **138**: mp= 94-95 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 12.44 (s, 1H), 8.20 (d, J = 10.8 Hz, 1H), 6.57 (d, J = 9.6 Hz, 1H), 3.98 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 202.0, 164.0, 156.2, 130.4, 129.6, 115.7, 102.5, 65.5, 32.6; IR (ATR) 3008, 2970, 1738, 1442, 1366, 1217, 1229, 1109 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_9\text{H}_{10}\text{NO}_5$ ($\text{M}+\text{H}^+$) 212.0559, found 212.0556.

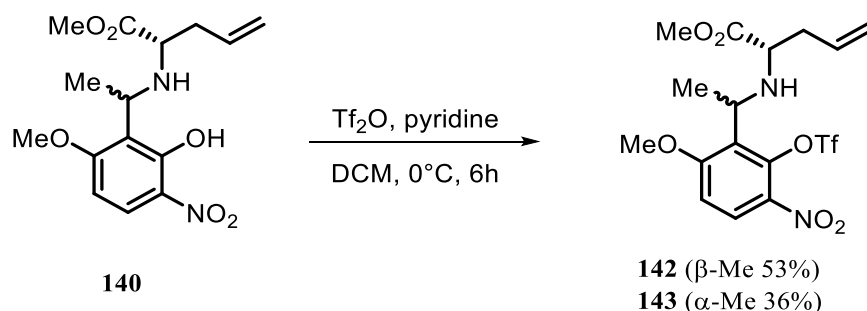


A solution of NH_4OH and MeOH (1:1, v/v) (20 mL) was added dropwise to **138** (973 mg, 4.61 mmol) at ambient temperature. The resulting mixture was stirred for 12 h and the solvents were removed under reduced pressure to obtain yellow solid. This crude imine was dissolved in dichloromethane (10 mL), and (S)-2-amino-4-pentenoic acid methyl ester hydrochloride (1.53 g, 9.22 mmol) and triethylamine (466 mg, 4.61 mmol) were added. The mixture was stirred under reflux for 12 h. Solvents were removed under reduced pressure and the crude product was dissolved in methanol (20 mL). To the stirred mixture at ambient temperature was added NaBH_4

(261 mg, 6.91 mmol) in one portion. The resulting mixture was stirred for 2h at ambient temperature. The solvent was removed under reduced pressure and the crude product was purified by chromatography (DCM: MeOH: NH₄OH, 100:2:1) to afford **140** as a mixture of diastereomers (1.16 g, 3.58 mmol, 78% overall) as yellow solid.

Analytical data for **140** as a mixture of diastereomers: mp = 104-106 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, *J* = 9.2 Hz, 1H), 7.96 (d, *J* = 9.6 Hz, 1H), 6.45 (d, *J* = 8.8 Hz, 1H), 6.42 (d, *J* = 9.6 Hz, 1H), 5.73 (m, 1H), 5.61 (m, 1H), 5.13 (m, 4H), 4.54 (q, *J* = 7.2 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.75 (s, 3H), 3.49 (s, 3H), 3.35 (t, *J* = 6.4 Hz, 1H), 3.29 (t, *J* = 6.0 Hz, 1H), 2.44 (m, 4H), 1.44 (d, *J* = 3.6 Hz, 3H), 1.42 (d, *J* = 4.0 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 173.8, 173.7, 163.0, 162.0, 155.2, 154.9, 133.0, 131.9, 131.2, 129.7, 126.5, 126.0, 119.4, 118.4, 118.3, 115.7, 102.7, 101.6, 77.2, 77.0, 76.8, 58.8, 58.4, 56.1, 56.0, 52.1, 51.6, 50.1, 47.9, 37.4, 36.8, 20.4, 19.7; IR (ATR) 3305, 2953, 2229, 2171, 1739, 1599, 1498, 1279, 1241, 1094, 925 cm⁻¹; HRMS (ESI) calcd for C₁₅H₂₁N₂O₆ (M+H⁺) 325.1400, found 325.1405

Analytical data for **140** (single isomer): [α]_D²¹ = -110.3 ± 0.1 (*c* = 0.1, MeOH); mp = 94-95 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, *J* = 9.6 Hz, 1H), 6.42 (d, *J* = 9.6 Hz, 1H), 5.62 (m, 1H), 5.13 (m, 2H), 4.37 (q, *J* = 7.2 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.29 (t, *J* = 6.0 Hz, 1H), 2.45 (t, *J* = 6.4 Hz, 2H), 1.43 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 173.7, 162.0, 155.2, 131.9, 131.3, 126.6, 119.5, 115.8, 101.6, 77.2, 77.0, 76.8, 58.4, 56.0, 52.1, 50.2, 37.4, 20.4; IR (ATR) 3305, 2953, 2848, 2531, 2196, 1735, 1596, 1497, 1276, 1237, 1014, 806 cm⁻¹; HRMS (ESI) calcd for C₁₅H₂₁N₂O₆ (M+H⁺) 325.1400, found 325.1405

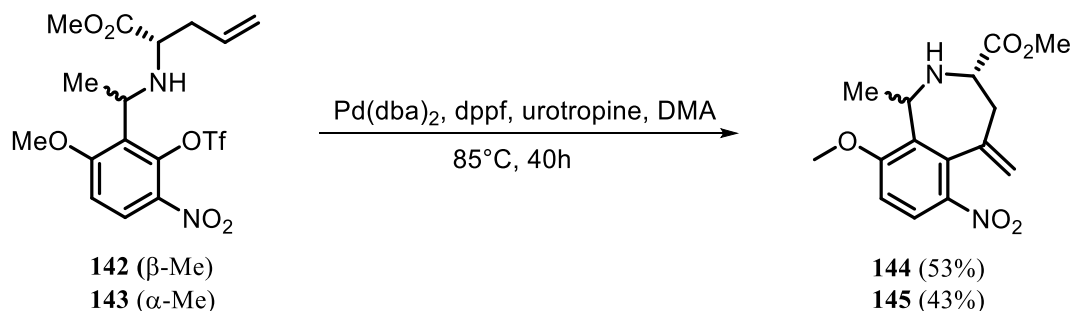


To a stirred solution of **140** (1.028 g, 3.17 mmol) in DCM (32 mL) under nitrogen at ambient temperature was added pyridine (627 mg, 7.92 mmol). The resulting mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (1.073 g, 3.80 mmol) was added dropwise. After stirring for 6 h at 0 °C, the reaction was quenched with saturated NH_4Cl solution (50 mL) and extracted with DCM (3×50 mL). The organic phases were combined, washed with 5% CuSO_4 solution (50 mL), dried (MgSO_4) and filtered. The filtrate was evaporated under reduced pressure and the crude product was purified by chromatography (EtOAc/hexane/AcOH, 50:50:1) affording, in the order of elution, **142** (622 mg, 1.36 mmol, 43%) as yellow oil and **143** (640 mg, 1.40 mmol, 44%) as yellow solid.

Analytical data for **142**: $[\alpha]_{\text{D}}^{21} = -131.6 \pm 0.1$ ($c = 0.03$, MeOH); ^1H NMR (400 MHz, CDCl_3) δ 7.96 (d, $J = 6.4$ Hz, 1H), 6.94 (d, $J = 6.0$ Hz, 1H), 5.72 (m, 1H), 5.04 (m, 2H), 4.21 (q, $J = 4.8$ Hz, 1H), 3.99 (s, 3H), 3.30 (s, 3H), 3.21 (t, $J = 4.8$ Hz, 1H), 2.33 (m, 2H), 1.51 (d, $J = 4.8$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 174.7, 163.3, 137.9, 135.9, 133.5, 128.4, 126.4, 121.4, 119.3, 117.7, 117.2, 115.0, 110.1, 77.2, 77.0, 76.8, 60.1, 56.6, 51.3, 50.7, 38.2, 19.9; IR (ATR) 2954, 2162, 1737, 1598, 1586, 1215 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_8\text{S}$ ($\text{M}+\text{H}^+$) 457.0893, found 457.0910

Analytical data for **143**: $[\alpha]_{\text{D}}^{21} = 27.9 \pm 0.1$ ($c = 0.04$, MeOH); mp = 68–69 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, $J = 6.0$ Hz, 1H), 6.97 (d, $J = 6.0$ Hz, 1H), 5.51 (m, 1H), 5.08 (m, 2H), 4.34 (q, $J = 4.8$ Hz, 1H), 3.98 (s, 3H), 3.74 (s, 3H), 3.01 (dd, $J = 6.0, 3.2$ Hz, 1H), 2.55 (br s, 1H), 2.43 (m,

1H), 2.29 (m, 1H), 1.54 (d, J = 4.8 Hz, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 174.0, 162.8, 138.6, 136.4, 133.6, 128.6, 126.6, 121.5, 119.3, 118.5, 117.2, 115.1, 109.9, 58.7, 56.5, 51.9, 49.5, 37.4, 19.5; IR (ATR) 2953, 2229, 2031, 1740, 1531, 1348, 1216 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_8\text{S}$ ($\text{M}+\text{H}^+$) 457.0893, found 457.0910



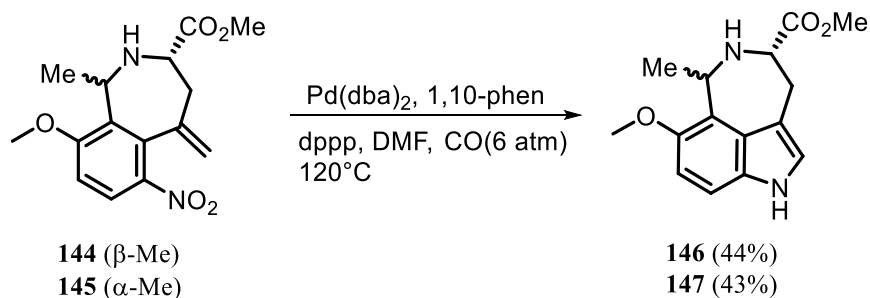
Urotropine (382 mg, 2.73 mmol), bis(diphenylphosphino)ferrocene (76 mg, 0.14 mmol), bis(dibenzylideneacetone)palladium (39 mg, 0.07 mmol) and *N,N*-dimethylacetamide (DMA) (10 mL) were added in a 50-mL round-bottomed flask. The mixture was stirred at ambient temperature for 5 minutes and a solution of **142** (622 mg, 1.36 mmol) in DMA (3.6 mL) was added under nitrogen. The resulting mixture was stirred at 90 °C for 48 h, cooled to ambient temperature and filtered through a pad of silica gel. The filtrate was washed with water (50 mL), dried (MgSO_4), filtered and the solvents were removed under reduced pressure. Purification of the crude product by chromatography (EtOAc/hexanes, 4:6) gave **144** (220 mg, 0.72mmol, 53%) as yellow solid.

Analytical data for **144**: $[\alpha]_{\text{D}}^{21} = -45.5 \pm 0.1$ (c = 0.02, MeOH); mp = 78-80 °C, ^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 9.2 Hz, 1H), 5.06 (m, 4H), 4.09 (dd, J = 11.2, 3.2 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.04 (dd, J = 12.8, 3.2 Hz, 1H), 2.50 (br s, 1H), 2.25 (br s, 1H), 1.37 (d, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 173.4, 157.6, 144.1, 142.4, 137.3, 133.8, 123.5, 117.9, 108.7, 77.2, 77.0, 76.8, 56.7, 56.1, 52.2, 46.9, 41.1, 17.0; IR (ATR) 2970,

2229, 1738, 1574, 1520, 1353, 1217 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 307.1294, found 307.1292

Urotropine (393 mg, 2.80 mmol), bis(diphenylphosphino) ferrocene (78 mg, 0.14 mmol), bis(dibenzylideneacetone)palladium (40 mg, 0.07 mmol) and N, N-dimethylacetamide (DMA)(5 mL) were added in a 50 mL round-bottomed flask. The mixture was stirred at ambient temperature for 10 minutes and a solution of **143** (640 mg, 1.40 mmol) in DMA (9 mL) was added under nitrogen. The resulting mixture was stirred at 90 °C for 48 h, cooled to ambient temperature and filtered through a pad of silica gel. The filtrate was washed with water (50 mL), dried (MgSO_4), filtered and the solvents were removed under reduced pressure. Purification of the crude product by chromatography (EtOAc/hexanes, 4:6) gave **145** (183 mg, 0.60 mmol, 43%) as yellow oil.

Analytical data for **145**: $[\alpha]_{\text{D}}^{21} = 11.6 \pm 0.1$ ($c = 0.02$, MeOH); ^1H NMR (400 MHz, CDCl_3) δ 7.66 (d, $J = 9.2$ Hz, 1H), 6.81 (d, $J = 9.2$ Hz, 1H), 5.14 (s, 1H), 4.92 (s, 1H), 4.60 (q, $J = 6.4$ Hz, 1H), 3.86 (s, 3H), 3.69 (s, 3H), 3.53 (dd, $J = 11.2, 6.4$ Hz, 1H), 3.26 (ddt, $J = 14.0, 6.0, 2.0$ Hz, 1H), 2.70 (dd, $J = 13.6, 11.2$ Hz, 1H), 1.29 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 159.2, 143.3, 140.7, 133.7, 132.1, 123.8, 118.3, 108.9, 77.3, 77.0, 76.7, 55.9, 54.6, 53.1, 52.1, 41.4, 21.6; IR (ATR) 2971, 2205, 1737, 1712, 1518, 1219, 996 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 307.1294, found 307.1291

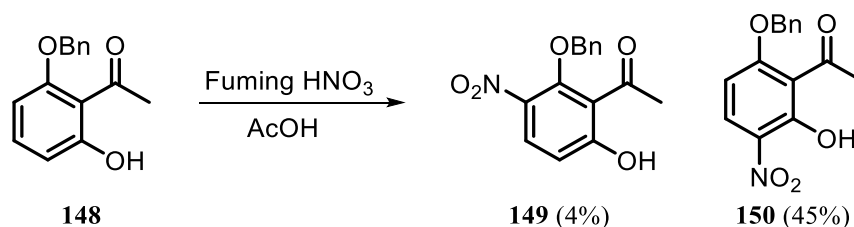


A solution of **144** (106 mg, 0.35 mmol), bis(dibenzylideneacetone)palladium (14 mg, 0.024 mmol), 1,3-bis(diphenylphosphino)propane (10 mg, 0.024 mmol), and 1,10-phenanthroline (9 mg, 0.048 mmol) in anhydrous *N, N*-dimethylformamide (3.5 mL), in an ACE-Glass pressure tube fitted with a pressure head, was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120 °C for 72 h. The mixture was cooled to ambient temperature, filtered through a pad of silica gel and the filtrate was evaporated under reduced pressure. The resulting residue was purified by chromatography (hexanes/EtOAc, 1:1) to afford **146** (42 mg, 0.15 mmol, 44%) as yellow solid.

Analytical data for **146**: $[\alpha]_D^{21} = 66.7 \pm 0.1$ ($c = 0.003$, MeOH); mp= 126-127 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 1H), 7.16 (d, $J = 8.8$ Hz, 1H), 7.00 (s, 1H), 6.87 (d, $J = 8.8$ Hz, 1H), 4.99 (q, $J = 6.8$ Hz, 1H), 4.17 (dd, $J = 12.0, 2.8$ Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.55 (dd, $J = 15.2, 2.8$ Hz, 1H), 3.01 (m, 1H), 1.49 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.1, 149.0, 132.6, 127.6, 124.9, 122.7, 112.5, 109.0, 108.5, 77.3, 77.0, 76.7, 57.1, 54.0, 52.3, 51.5, 34.6, 19.9; IR (ATR) 3650, 3003, 2003, 1739, 1439, 1366, 1231, 1216 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 275.1396, found 275.1401.

A solution of **145** (194 mg, 0.63 mmol), bis(dibenzylideneacetone)palladium (25 mg, 0.044 mmol), 1,3- bis(diphenylphosphino)propane (18 mg, 0.044 mmol), and 1,10-phenanthroline (16 mg, 0.089 mmol) in anhydrous *N, N*-dimethylformamide (6 mL), in an ACE-Glass pressure tube fitted with a pressure head, was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120 °C for 72 h. The mixture was cooled to ambient temperature, filtered through a pad of silica gel and the filtrate was evaporated under reduced pressure. The resulting residue was purified by chromatography (hexanes/EtOAc, 1:1) to afford **147** (75 mg, 0.27 mmol, 43%) as yellow solid.

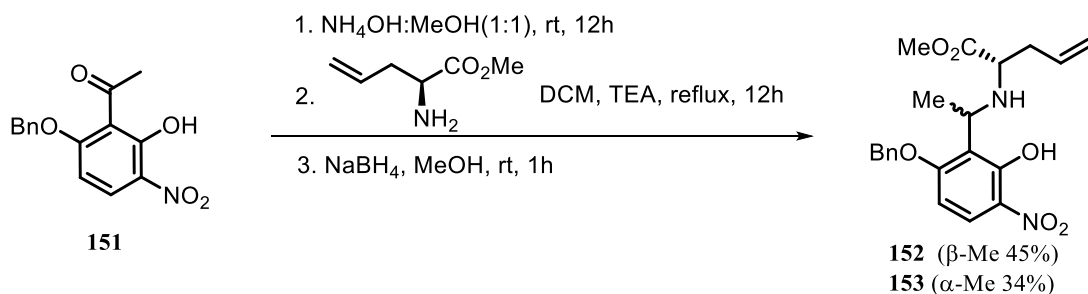
Analytical data for **147**: $[\alpha]_D^{21} = -8.3 \pm 0.1 (c = 0.012, \text{MeOH})$; mp = 141-143 °C, ^1H NMR (400 MHz, CDCl_3) δ 7.96 (br s, 1H), 7.17 (d, $J = 8.4$ Hz, 1H), 7.00 (br s, 1H), 6.88 (d, $J = 8.4$ Hz, 1H), 4.68 (q, $J = 6.4$ Hz, 1H), 3.87 (dd, $J = 11.8, 2.8$ Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.37 (dd, $J = 15.2, 2.8$ Hz, 1H), 3.17 (m, 1H), 1.58 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.1, 150.2, 132.7, 126.7, 125.7, 122.7, 112.8, 109.2, 109.2, 77.3, 77.0, 76.7, 59.0, 57.0, 54.0, 52.2, 34.3, 23.7; IR (ATR) 3823, 3675, 3651, 1983, 1512, 1363, 1235; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 275.1396, found 275.1400



1-[2-Hydroxy-6-(phenylmethoxy)phenyl]ethanone (**148**) (1.54 g, 6.3 mmol) was dissolved in glacial acetic acid (6.3 mL) and fuming nitric acid (0.6 mL) was added dropwise. The reaction mixture was stirred in a round-bottomed flask equipped with a drying tube (CaCl_2) at room temperature for 40 min, and then at 50 °C for 16 h. The reaction mixture was poured into ice-water (40 mL) and extracted with EtOAc (3×40 mL). The combined organic layers were dried (MgSO_4), filtered and solvents were removed under reduced pressure. The crude product was purified by chromatography (EtOAc/hexane, 2:8) affording, in the order of elution, **149** (96 mg, 0.33 mmol, 5%) as a yellow solid and **150** (837 mg, 2.91 mmol, 46%) as yellow solid.

Analytical data for **149**: mp = 103-104 °C; ^1H NMR (400 MHz, CDCl_3) δ 13.13 (s, 1H), 8.10 (d, $J = 12.0$ Hz, 1H), 7.41 (m, 5H), 6.83 (d, $J = 8.0$ Hz, 1H), 5.06 (s, 2H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 205.0, 167.3, 156.4, 134.6, 132.5, 129.2, 128.8, 128.7, 115.9, 114.5, 79.4, 32.8; IR (ATR) 2933, 2189, 1631, 1593, 1456, 1365, 1053, 969, 831cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{NO}_5$ ($\text{M}+\text{H}^+$) 288.0872, found 288.0867

Analytical data for **150**: mp= 123-124 °C; ^1H NMR (400 MHz, CDCl_3) δ 12.38 (s, 1H), 8.16 (d, J = 9.6 Hz, 1H), 7.39 (m, 5H), 6.61 (d, J = 9.6 Hz, 1H), 5.23 (s, 2H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.3, 162.8, 155.9, 134.6, 130.0, 129.7, 128.9, 128.8, 127.4, 117.3, 104.0, 71.5, 32.8; IR (ATR) 3071, 3039, 2628, 2193, 1623, 1588, 1367, 1319, 1246, 990, 777 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{NO}_5$ ($\text{M}+\text{H}^+$) 288.0872, found 288.0868

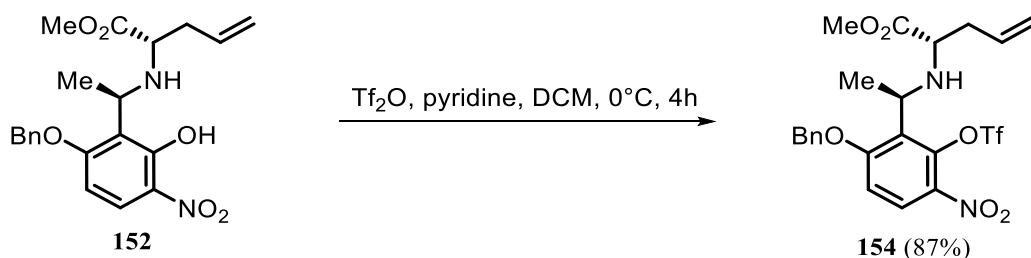


A solution of NH_4OH and MeOH (1:1, v/v) (20 mL) was added dropwise to **150** (1.675 g, 5.83 mmol) at ambient temperature. The resulting mixture was stirred for 12 h and the solvents were removed under reduced pressure to obtain yellow solid. This crude imine was dissolved in dichloromethane (30 mL), and (S)-2-amino-4-pentenoic acid methyl ester hydrochloride (1.931 g, 11.66 mmol) and triethylamine (590 mg, 5.83 mmol) were added. The mixture was stirred under reflux for 12 h. Solvents were removed under reduced pressure and the crude product was dissolved in methanol (30 mL). To the stirred mixture at ambient temperature was added NaBH_4 (331 mg, 8.75 mmol) in one portion. The resulting mixture was stirred for 2 h at ambient temperature. The solvent was removed under reduced pressure and the crude product was purified by chromatography (EtOAc/hexane, 2:8) affording, in the order of elution, **152** (1.053 g, 2.63 mmol, 45%) and **153** (798 mg, 1.99 mmol, 34%) as yellow solids.

Analytical data for **152**: $[\alpha]_{\text{D}}^{21} = -2.1 \pm 0.1$ (c = 0.05, MeOH); mp= 110-112 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, J = 9.6 Hz, 1H), 7.39 (m, 5H), 6.55 (d, J = 9.2 Hz, 1H), 5.71 (m, 1H),

5.16 (m, 2H), 5.07 (m, 2H), 4.59 (q, J = 6.8 Hz, 1H), 3.47 (s, 3H), 3.37 (t, J = 6.4 Hz, 1H), 2.42 (t, J = 6.8 Hz, 2H), 1.44 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 162.2, 155.1, 135.5, 132.9, 129.7, 128.9, 128.8, 128.5, 127.5, 127.4, 126.0, 118.7, 118.4, 104.0, 71.0, 58.9, 51.6, 48.0, 36.8, 19.8.; IR (ATR) 3649, 2952, 2033, 1737, 1592, 1435, 1275, 1238 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}^+$) 401.1713, found 401.1717

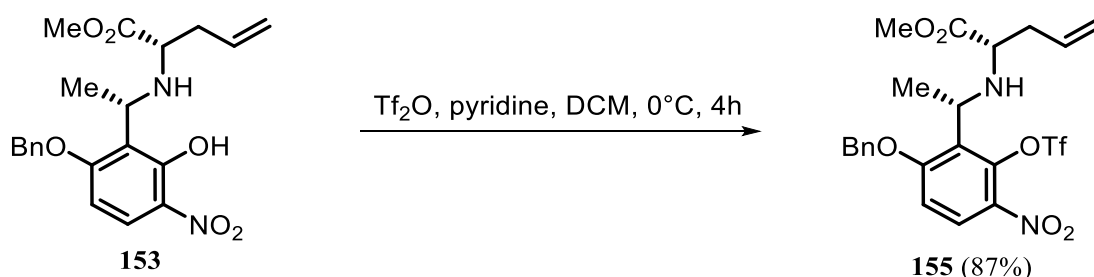
Analytical data for **153**: $[\alpha]_{\text{D}}^{21} = -21.6 \pm 0.1$ (c = 0.05, MeOH); mp = 109–110 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.95 (d, J = 9.6 Hz, 1H), 7.38 (m, 5H), 6.48 (d, J = 9.6 Hz, 1H), 5.62 (m, 1H), 5.15 (m, 4H), 4.49 (q, J = 6.8 Hz, 1H), 3.69 (s, 3H), 3.32 (t, J = 6.4 Hz, 1H), 2.45 (t, J = 6.0 Hz, 2H), 1.48 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.7, 161.0, 155.3, 135.7, 131.8, 128.9, 128.8, 128.4, 127.4, 127.0, 126.5, 119.6, 116.1, 110.0, 102.9, 70.6, 58.5, 52.1, 50.2, 37.4, 20.4; IR (ATR) 3650, 3305, 2953, 2173, 1910, 1736, 1597, 1276 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}^+$) 401.1713, found 401.1718



To a stirred solution of **152** (1.053 g, 2.63 mmol) in DCM (26 mL) under nitrogen at ambient temperature was added pyridine (520 mg, 6.58 mmol). The resulting mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (890 mg, 3.16 mmol) was added dropwise. After stirring for 4 h at 0 °C, the reaction was quenched with saturated NH_4Cl solution (25 mL) and extracted with DCM (3×50 mL). The organic phases were combined, washed with 5% CuSO_4 solution (50 mL), dried (MgSO_4) and filtered. The filtrate was evaporated under reduced

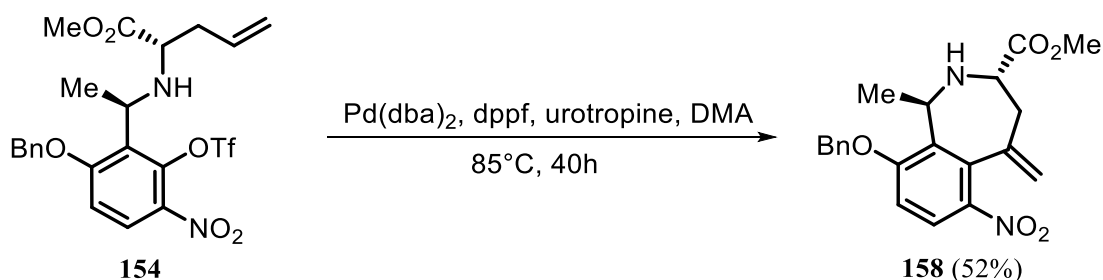
pressure and the crude product was purified by chromatography (EtOAc/hexane, 2:8) affording **154** (1.223 g, 2.30 mmol, 87%) as yellow oil.

Analytical data for **154**: $[\alpha]_D^{21} = 75.8 \pm 0.1$ ($c = 0.03$, MeOH); ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, $J = 10.0$ Hz, 1H), 7.48 (m, 5H), 7.03 (d, $J = 9.2$ Hz, 1H), 5.68 (m, 1H), 5.22 (s, 2H), 5.02 (m, 2H), 4.24 (q, $J = 7.2$ Hz, 1H), 3.34 (s, 3H), 3.25 (t, $J = 6.4$ Hz, 1H), 2.83 (br s, 1H), 2.33 (t, $J = 6.4$ Hz, 2H), 1.51 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 174.8, 162.5, 138.0, 136.1, 134.5, 133.2, 129.0, 129.0, 128.6, 128.2, 126.4, 123.0, 119.9, 117.9, 116.7, 113.5, 111.0, 77.3, 77.0, 76.7, 72.1, 60.1, 51.4, 50.7, 38.2, 20.1; IR (ATR) 3464, 3004, 2949, 1737, 1433, 1365, 1227 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_8\text{S}$ ($\text{M} + \text{H}^+$) 533.1206, found 533.1230



To a stirred solution of **153** (798 mg, 1.99 mmol) in DCM (20 mL) under nitrogen at ambient temperature was added pyridine (394 mg, 4.98 mmol). The resulting mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (675 mg, 2.39 mmol) was added dropwise. After stirring for 4 h at 0 °C, the reaction was quenched with saturated NH_4Cl solution (25 mL) and extracted with DCM (3×50 mL). The organic phases were combined, washed with 5% CuSO_4 solution (50 mL), dried (MgSO_4) and filtered. The filtrate was evaporated under reduced pressure and the crude product was purified by chromatography (EtOAc/hexanes, 2:8) affording **155** (918 mg, 1.72 mmol, 87%) as yellow oil.

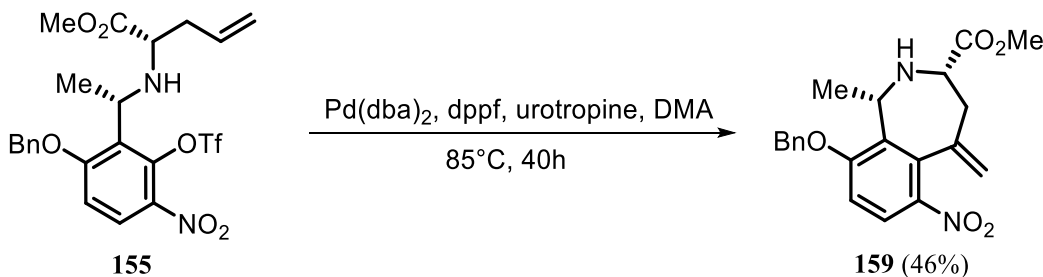
Analytical data for **155**: $[\alpha]_D^{21} = -2.7 \pm 0.1 (c = 0.04, \text{MeOH})$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.02 (d, $J = 9.2$ Hz, 1H), 7.43 (m, 5H), 7.05 (d, $J = 10.4$ Hz, 1H), 5.47 (m, 1H), 5.21 (m, 2H), 4.96 (m, 2H), 4.32 (q, $J = 6.8$ Hz, 1H), 3.70 (s, 3H), 3.05 (dd, $J = 8.4, 5.6$ Hz, 1H), 2.38 (m, 1H), 2.24 (m, 1H), 1.56 (d, $J = 8.0$ Hz, 3H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 173.9, 161.9, 138.6, 136.4, 134.2, 133.3, 129.0, 129.0, 128.7, 127.6, 126.6, 123.0, 119.9, 118.6, 116.7, 113.5, 111.1, 71.8, 58.9, 51.9, 49.4, 37.4, 19.6; IR (ATR) 3467, 3016, 2971, 2952, 1740, 1365, 1228, 1029 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_8\text{S}$ ($\text{M} + \text{H}^+$) 533.1206, found 533.1234



Urotropine (581 mg, 4.14 mmol), bis(diphenylphosphino) ferrocene (115 mg, 0.21 mmol), bis(dibenzylideneacetone)palladium (60 mg, 0.10 mmol) and *N,N*-dimethylacetamide (DMA) (5 mL) were added in a 50-mL round-bottomed flask. The mixture was stirred at ambient temperature for 10 minutes and a solution of **154** (1.103 g, 2.07 mmol) in DMA (15 mL) was added under nitrogen. The resulting mixture was stirred at 90 °C for 48 h, cooled to ambient temperature and filtered through a pad of silica gel. The filtrate was washed with brine (50 mL), dried (MgSO_4), filtered and the solvents were removed under reduced pressure. Purification of the crude product by chromatography (EtOAc/hexanes, 4:6) gave **158** (414 mg, 1.08 mmol, 52%) as yellow oil.

Analytical data for **158**: $[\alpha]_D^{21} = -235.3 \pm 0.1 (c = 0.007, \text{MeOH})$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.58 (d, $J = 8.8$ Hz, 1H), 7.37 (m, 5H), 6.84 (d, $J = 9.2$ Hz, 1H), 5.18 (m, 4H), 4.96 (s, 1H), 4.12

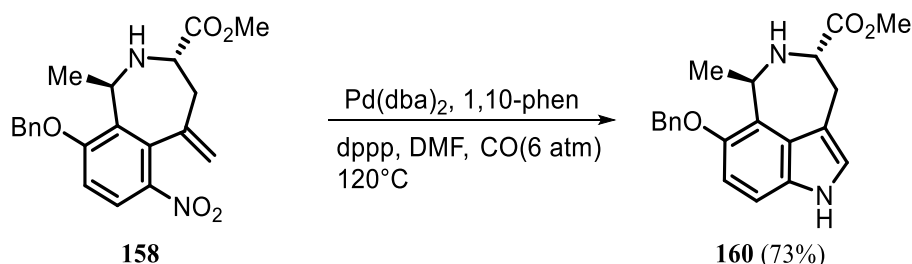
(dd, J = 11.2, 2.8 Hz, 1H), 3.76 (s, 3H), 3.09 (dd, J = 12.4, 3.2 Hz, 1H), 2.54 (br s, 1H), 2.08 (br s, 1H), 1.42 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 173.3, 156.6, 144.3, 142.3, 139.9, 137.4, 135.8, 134.2, 128.7, 128.3, 127.1, 123.5, 118.0, 110.1, 77.3, 77.0, 76.7, 70.8, 56.6, 52.2, 47.2, 41.0, 17.1; IR (ATR) 3462, 3015, 2971, 2946, 1738, 1365, 1217 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 383.1607, found 383.1617



Urotropine (483 mg, 3.45 mmol), bis(diphenylphosphino) ferrocene (96 mg, 0.17 mmol), bis(dibenzylideneacetone)palladium (50 mg, 0.08 mmol) and N, N-dimethylacetamide (DMA) (5 mL) were added in a 50-mL round-bottomed flask. The mixture was stirred at ambient temperature for 10 minutes and a solution of **155** (918 mg, 1.72 mmol) in DMA (12 mL) was added under nitrogen. The resulting mixture was stirred at 90 °C for 48 h, cooled to ambient temperature and filtered through a pad of silica gel. The filtrate was washed with brine (50 mL), dried (MgSO_4), filtered and the solvents were removed under reduced pressure. Purification of the crude product by chromatography (EtOAc/hexanes, 4:6) gave **159** (303 mg, 0.79 mmol, 46%) as yellow oil.

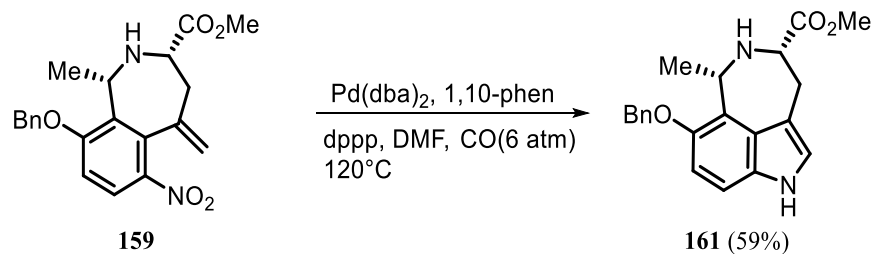
Analytical data for **159**: $[\alpha]_{\text{D}}^{21} = -14.5 \pm 0.1$ (c = 0.014, MeOH); ^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, J = 9.2 Hz, 1H), 7.37 (m, 5H), 6.90 (d, J = 9.2 Hz, 1H), 5.15 (m, 3H), 4.98 (s, 1H), 4.77 (q, J = 6.4 Hz, 1H), 3.74 (s, 3H), 3.60 (dd, J = 11.2, 6.4 Hz, 1H), 3.32 (dd, J = 14.0, 6.4 Hz, 1H), 2.75 (dd, J = 13.8, 11.6 Hz, 1H), 1.64 (br s, 1H), 1.38 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 174.1, 158.2, 143.6, 140.7, 135.6, 133.9, 132.5, 128.7, 128.3, 126.9, 123.9, 118.5,

110.1, 77.3, 77.0, 76.7, 70.5, 54.7, 53.3, 52.2, 41.5, 21.8; IR (ATR) 3464, 3349, 3005, 2971, 1738, 1519, 1352, 1217 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 383.1607, found 383.1615



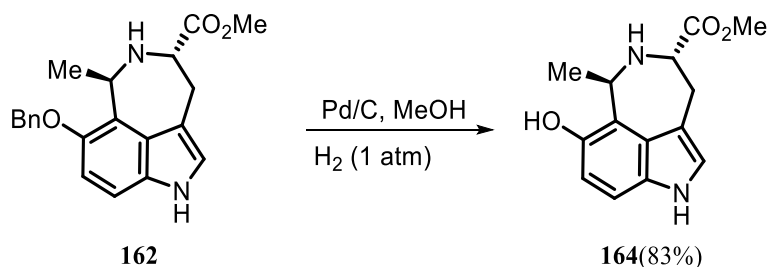
A solution of **158** (75 mg, 0.196 mmol), bis(dibenzylideneacetone)palladium (8 mg, 0.014 mmol), 1,3-bis(diphenylphosphino)propane (6 mg, 0.014 mmol), and 1,10-phenanthroline (5 mg, 0.027 mmol) in anhydrous *N,N*-dimethylformamide (2 mL), in an ACE-Glass pressure tube fitted with a pressure head, was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120 °C for 72 h. The mixture was cooled to ambient temperature, filtered through a pad of silica gel and the filtrate was evaporated under reduced pressure. The resulting residue was purified by chromatography (hexanes/EtOAc, 6:4) to afford **160** (50 mg, 0.143 mmol, 73%) as white solid.

Analytical data for **160**: $[\alpha]_{\text{D}}^{21} = +16.7 \pm 0.1$ ($c = 0.012$, MeOH); mp= 163-164 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.19 (br s, 1H), 7.39 (m, 5H), 7.14 (d, $J = 9.2$ Hz, 1H), 6.98 (br s, 1H), 6.91 (d, $J = 8.8$ Hz, 1H), 5.12 (m, 3H), 4.20 (dd, $J = 12.2, 2.8$ Hz, 1H), 3.81(s, 3H), 3.56 (dd, $J = 15.6, 2.4$ Hz, 1H), 3.03 (ddd, $J = 15.4, 12.4, 1.6$ Hz, 1H), 2.32 (br s, 2H), 1.55 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.0, 148.0, 138.1, 132.8, 128.4, 128.1, 127.6, 127.6, 127.2, 127.0, 124.9, 122.8, 112.5, 109.9, 109.2, 77.3, 77.0, 76.7, 71.8, 54.0, 52.3, 51.6, 34.5, 20.1; IR (ATR) 3823, 3675, 3651, 1983, 1512, 1363, 1235; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 351.1709, found 351.1716



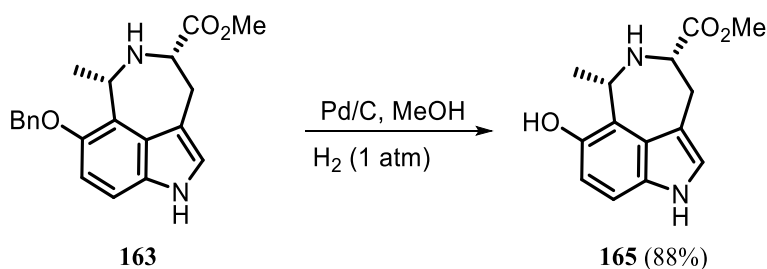
A solution of **159** (120 mg, 0.314 mmol), bis(dibenzylideneacetone)palladium (13 mg, 0.022 mmol), 1,3-bis(diphenylphosphino)propane (9 mg, 0.022 mmol), and 1,10-phenanthroline (8 mg, 0.044 mmol) in anhydrous *N,N*-dimethylformamide (3.1 mL), in an ACE-Glass pressure tube fitted with a pressure head, was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120 °C for 72 h. The mixture was cooled to ambient temperature, filtered through a pad of silica gel and the filtrate was evaporated under reduced pressure. The resulting residue was purified by chromatography (hexanes/EtOAc, 6:4) to afford **161** (65 mg, 0.185 mmol, 59%) as white solid.

Analytical data for **161**: $[\alpha]_D^{21} = -25.0 \pm 0.1$ ($c = 0.008$, MeOH); mp = 151-152 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.92 (br s, 1H), 7.34 (m, 5H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.02 (br s, 1H), 6.94 (d, $J = 8.8$ Hz, 1H), 5.09 (dd, $J = 16.4, 12.0$ Hz, 2H), 4.78 (q, $J = 6.4$ Hz, 1H), 3.89 (dd, $J = 12.0, 2.8$ Hz, 1H), 3.79 (s, 3H), 3.39 (dd, $J = 15.2, 2.8$ Hz, 1H), 3.21 (ddd, $J = 15.4, 11.6, 1.6$ Hz, 1H), 1.62 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.0, 149.2, 138.0, 132.9, 128.4, 127.6, 127.4, 127.2, 125.8, 122.7, 113.0, 110.7, 109.3, 77.3, 77.0, 76.7, 72.1, 59.0, 53.9, 52.2, 34.1, 23.9; IR (ATR) 3823, 3675, 3651, 1983, 1512, 1363, 1235; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 351.1709, found 351.1699



To a solution of **162** (50 mg, 0.14 mmol) in methanol in an ACE-Glass pressure tube was added Pd/C (10%) (7 mg, 0.007 mmol). The resulting mixture was saturated with hydrogen gas (3 cycles to 2.7 atm) and stirred at 60 °C for 12 h. The reaction mixture was filtered through celite and the filtrate obtained was concentrated under reduced pressure. Purification of the crude product using MeOH/CHCl₃ (1:4) afforded **164** (30 mg, 0.12 mmol, 83%) as an amorphous white powder.

Analytical data for **164**: $[\alpha]_{\text{D}}^{21} = -20.0 \pm 0.1$ ($c = 0.005$, MeOH); mp = 168-170 °C (lit: 183-185 °C) ¹H NMR (400 MHz, DMSO-D₆) δ 10.54 (br s, 1H), 8.44 (s, 1H), 7.02 (s, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 4.70 (q, $J = 6.8$ Hz, 1H), 3.95 (d, $J = 10.8$ Hz, 1H), 3.68 (s, 3H), 3.32 (d, $J = 14.8$ Hz, 1H), 2.87 (dd, $J = 14.4, 11.6$ Hz, 1H), 1.34 (d, $J = 6.8$ Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.0, 144.4, 132.4, 125.1, 125.0, 122.4, 112.6, 112.2, 109.3, 54.0, 52.3, 51.5, 34.5, 19.5; IR (ATR) 3698, 3671, 3622, 2111, 1519, 1356, 1245; HRMS (ESI) calcd for C₁₄H₁₇N₂O₃ (M+H⁺) 261.1239, found 261.1237

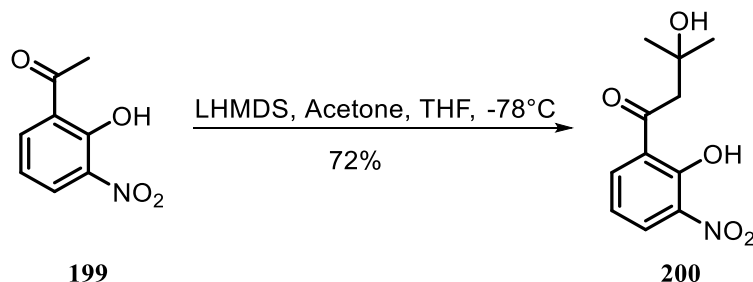


To a solution of **163** (46 mg, 0.13 mmol) in methanol in an ACE-Glass pressure tube was added Pd/C (10%) (7 mg, 0.007 mmol). The resulting mixture was saturated with hydrogen gas

(3 cycles to 2.7 atm) and stirred at room temperature for 1 h. The reaction mixture was filtered through celite and the filtrate obtained was concentrated under reduced pressure. Purification of the crude product using MeOH/CHCl₃ (1:4) afforded **165** (30 mg, 0.12 mmol, 88%) as an amorphous white powder.

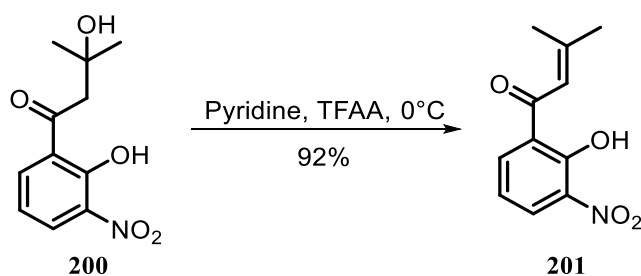
Analytical data for **165**: $[\alpha]_D^{21} = -40.0 \pm 0.1$ ($c = 0.005$, MeOH); mp= 91-93 °C (lit: 80-83 °C) ¹H NMR (400 MHz, CDCl₃) δ 7.93 (brs, 1H), 7.07 (d, $J = 8.8$ Hz, 1H), 7.00 (s, 1H), 6.65 (d, $J = 8.4$ Hz, 1H), 4.67 (q, $J = 6.4$ Hz, 1H), 3.87 (dd, $J = 11.4, 2.8$ Hz, 1H), 3.79 (s, 3H), 3.38 (dd, $J = 14.8, 2.8$ Hz, 1H), 3.16 (ddd, $J = 15.2, 11.8, 1.6$ Hz, 1H), 1.64 (d, $J = 6.4$ Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.0, 145.5, 132.5, 125.8, 123.9, 122.5, 112.9, 112.7, 109.4, 59.1, 54.0, 52.2, 34.5, 23.2; IR (ATR) 3823, 3693, 3652, 2031, 1566, 1341, 1254; HRMS (ESI) calcd for C₁₄H₁₇N₂O₃ (M+H⁺) 261.1239, found 261.1238

5.3 Supporting Information for Chapter 4: Aurantioclavine



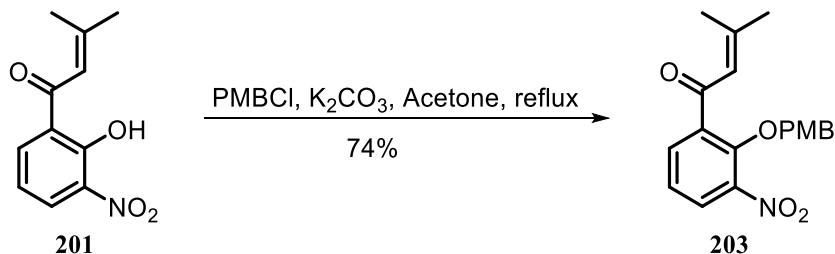
A solution of 2-hydroxy-3-nitroacetophenone **199** (513 mg, 2.83 mmol) in THF (15 mL) was added dropwise into a solution of LHMDS (1 M in THF) (11.3 mL, 11.3 mmol) at -78 °C under argon atmosphere. The resulting mixture was stirred at -78 °C for 1 h. To the stirred mixture was added acetone (2.1 mL, 28.32 mmol) dropwise and continued to stir for 3 h at -78 °C before quenching with saturated NH₄Cl solution (15 mL). The mixture was extracted with EtOAc (3×50 mL). The combined organic layers were dried (MgSO₄), filtered and solvents were removed under reduced pressure. The crude product was purified by chromatography (MeOH/DCM, 1:99) affording, **200** (490 mg, 2.05 mmol, 72%) as a yellow oil.

Analytical data for **200**: ¹H NMR (400 MHz, CDCl₃) δ 12.66 (br s, 1H), 8.22 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.08 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.05 (t, *J* = 8.4 Hz, 1H), 3.31 (br s, 1H), 3.25 (s, 2H), 1.37 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 204.7, 155.7, 137.2, 136.8, 131.2, 125.2, 118.7, 77.3, 77.0, 76.7, 70.2, 51.3, 29.6; IR (ATR) 3857, 3676, 3652, 2243, 1734, 1556, 1345; HRMS (ESI) calcd for C₁₁H₁₄NO₅ (M+H⁺) 240.0872, found 240.0869.



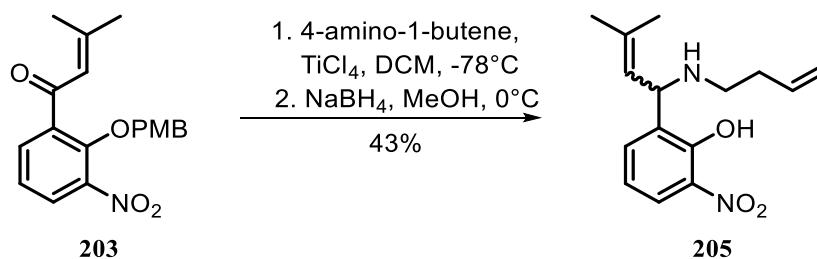
To a solution of **200** (1.13 g, 3.86 mmol) in pyridine (7.7 mL) under a nitrogen atmosphere was added trifluoroacetic anhydride (1.1 mL, 7.72 mmol) at 0 °C. The resulting mixture was stirred 0 °C for 4 h. The solvents were removed under reduced pressure and the crude product was purified by chromatography (EtOAc/hexanes, 5:95) affording **201** (784 mg, 3.54 mmol, 92%) as yellow solid.

Analytical data for **201**: mp= 70-71 °C; ¹H NMR (400 MHz, CDCl₃) δ 13.77(s, 1H), 8.13 (dd, *J*= 8.0, 1.6 Hz, 1H), 8.04 (dd, *J*= 8.4, 1.6 Hz, 1H), 6.98 (t, *J*= 8.0 Hz, 1H), 6.78 (m, 1H), 2.27 (d, *J*= 1.2 Hz, 3H), 2.09 (d, *J*= 1.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 194.5, 161.9, 157.0, 138.1, 135.3, 130.9, 124.0, 119.7, 117.8, 28.5, 21.8; IR (ATR) 3035, 2961, 2022, 1763, 1596, 1312, 1197cm⁻¹; HRMS (ESI) calcd for C₁₁H₁₂NO₄ (M+H⁺) 222.0766, found 222.0762.



To a solution of **201** (610 mg, 2.76 mmol) in acetone (28 mL) was added solid potassium carbonate (1.15 g, 8.29 mmol) and *p*-methoxybenzyl chloride (520 mg, 3.31 mmol). The resulting mixture was stirred under reflux for 54 h. After cooling at ambient temperature, the reaction mixture was filtered through celite. The solvents were removed from the filtrate under reduced pressure. Water (50 mL) was added to the crude residue and the resulting mixture was extracted with EtOAc (3×80 mL). Organic layers were combined and dried (MgSO₄), filtered and the filtrate was evaporated under reduced pressure. The crude product was purified by chromatography (5% K₂CO₃ added to silica gel, EtOAc/hexane, 5:95) affording **203** (700 mg, 2.05 mmol, 74%) as yellow oil.

Analytical data for **203**: ^1H NMR (400 MHz, DMSO- D_6) δ 8.05 (dd, J = 8.0, 2.0 Hz, 1H), 7.78 (dd, J = 7.6, 1.6 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.21 (m, 2H), 6.93 (m, 2H), 6.57 (m, 1H), 4.86 (s, 2H), 3.76 (s, 3H), 2.20 (d, J = 1.2 Hz, 3H), 1.92 (d, J = 1.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO- D_6) δ 190.6, 160.0, 159.3, 149.0, 145.2, 138.0, 134.1, 130.7, 127.8, 127.5, 125.4, 124.2, 114.3, 114.0, 78.6, 55.6, 28.0, 21.5; IR (ATR) 3041, 2974, 1898, 1740, 1586, 1336 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_5$ ($\text{M}+\text{H}^+$) 342.1342, found 342.1336.



To a mixture of **203** (360 mg, 1.05 mmol) in DCM (5 mL) was added 4-amino-1-butene (450 mg, 6.33 mmol). The resulting mixture was cooled to -78°C and TiCl_4 (1M in DCM) (1.2 mL, 1.2 mmol) solution was added dropwise. After stirring at -78°C for 4 h, NaBH_4 (60 mg, 1.58 mmol) and methanol (5 mL) were added. The resulting mixture was allowed to warm to 0°C and stirred for 1 h. To the stirred mixture was added 0.5N NaOH (20 mL) and extracted with EtOAc (3 \times 50 mL). The combined organic layers were dried (MgSO_4), filtered and solvents were removed under reduced pressure. The crude product was purified by chromatography (EtOAc/hexane, 2:8) affording **205** (126 mg, 0.46 mmol, 43%) as a yellow solid.

Analytical data for **205**: mp= $128\text{--}130^\circ\text{C}$; δ 7.85 (dd, J = 8.4, 1.6 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 6.77 (t, J = 7.6 Hz, 1H), 5.76 (m, 1H), 5.34 (dt, J = 9.6, 1.6 Hz, 1H), 5.12 (m, 2H), 4.74 (d, J = 9.2 Hz, 1H), 2.73 (m, 2H), 2.33 (m, 2H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.9, 136.8, 135.0, 133.6, 129.9, 124.7, 123.3, 117.6, 117.5, 58.9, 45.5, 33.4, 25.8, 18.3; IR (ATR)

3352, 2973, 2221, 1833, 1586, 1456, 1243, 1053 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_3$
($\text{M}+\text{H}^+$) 277.1552, found 277.1551

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Appendix

^1H and ^{13}C NMR Spectra

- ^1H and ^{13}C NMR for Chapter 2: Cimitrypazepine and Fargesine 91
- ^1H and ^{13}C NMR for Chapter 3: Hyrtioreticulins C & D 113
- ^1H and ^{13}C NMR for Chapter 4: Aurantioclavine 165

^1H and ^{13}C NMR for Chapter 2: Cimitrypazepine and Fargesine

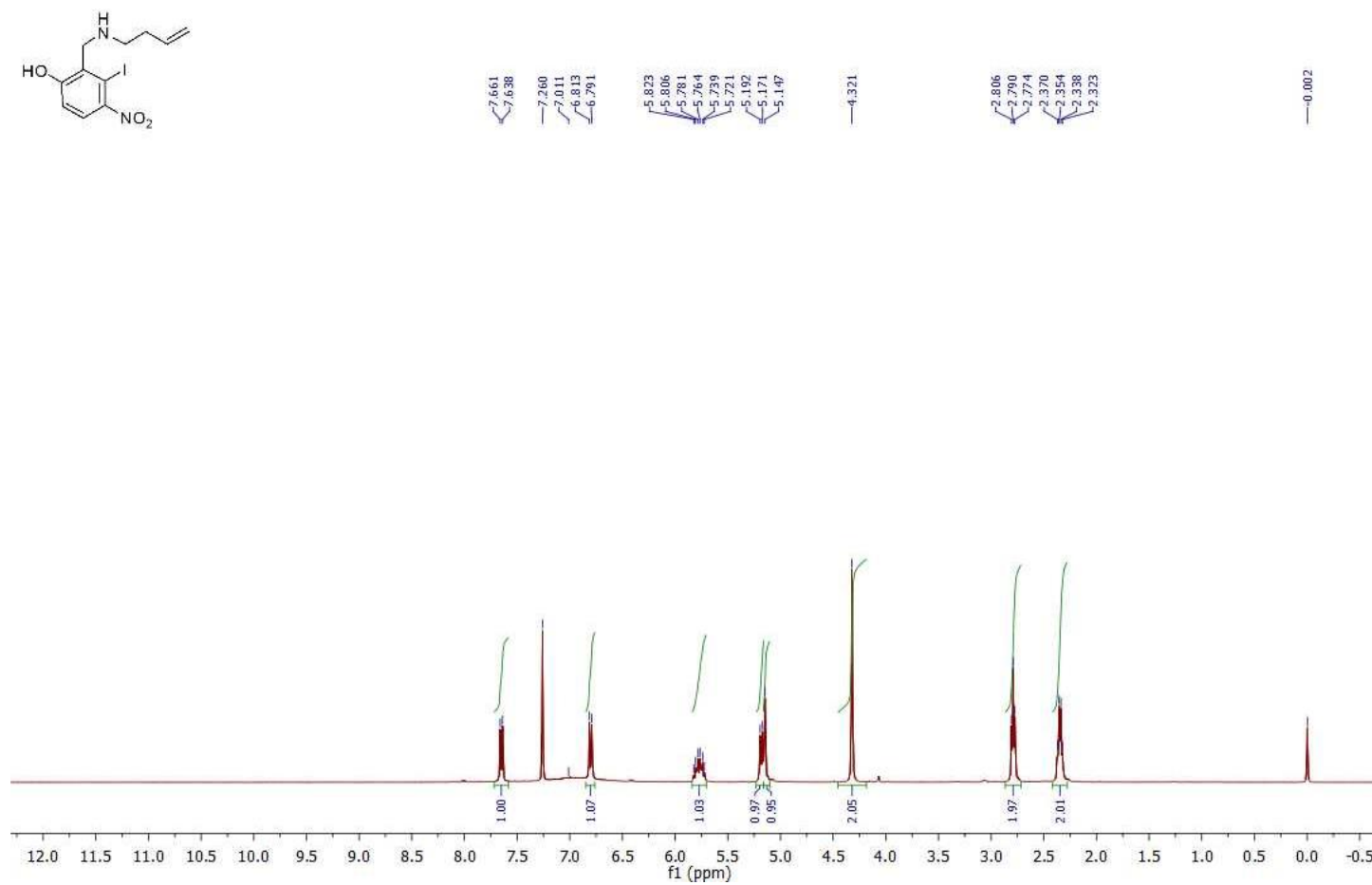


Figure 9: ^1H NMR of Compound 95

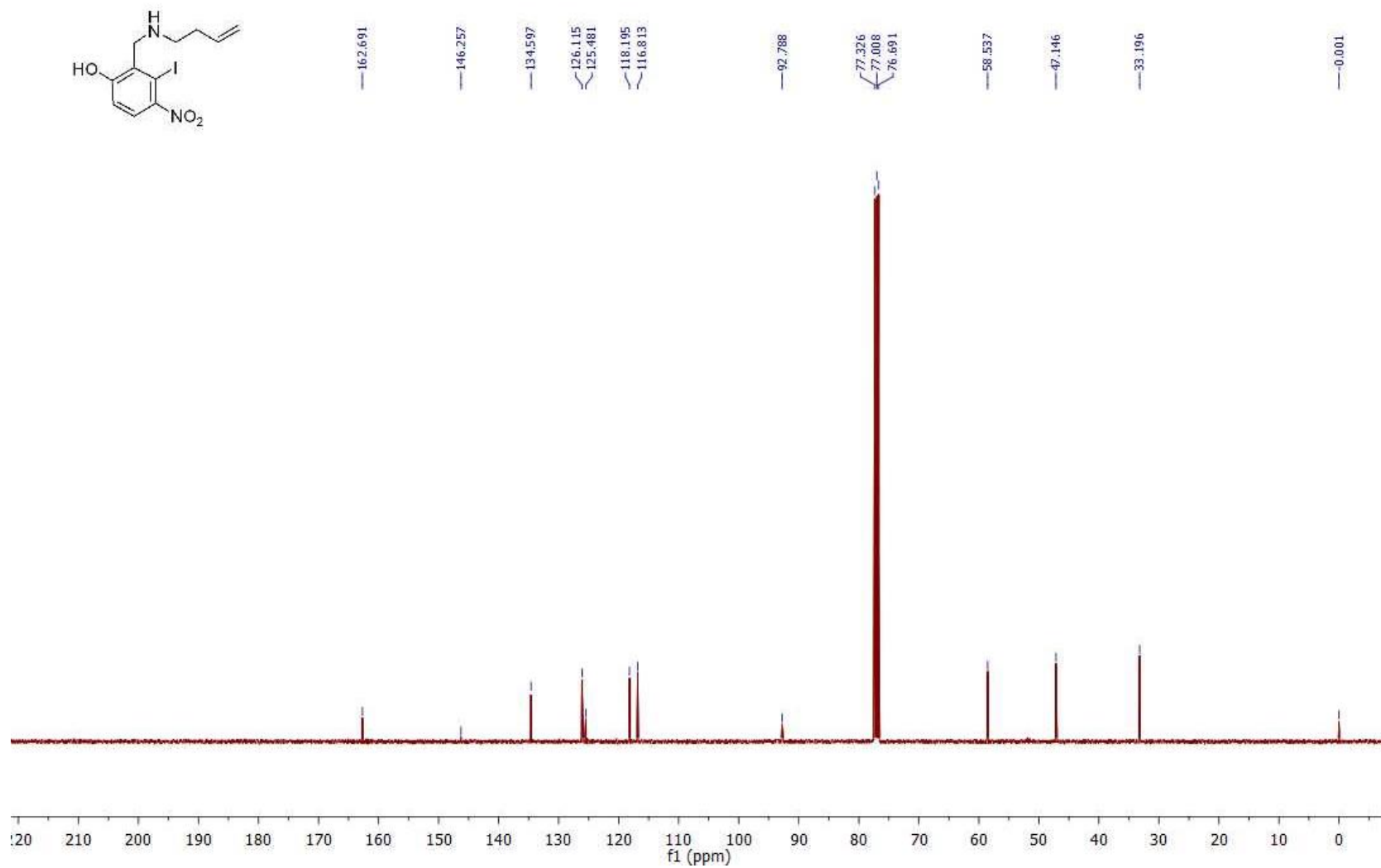


Figure 10: ^{13}C NMR of Compound **95**

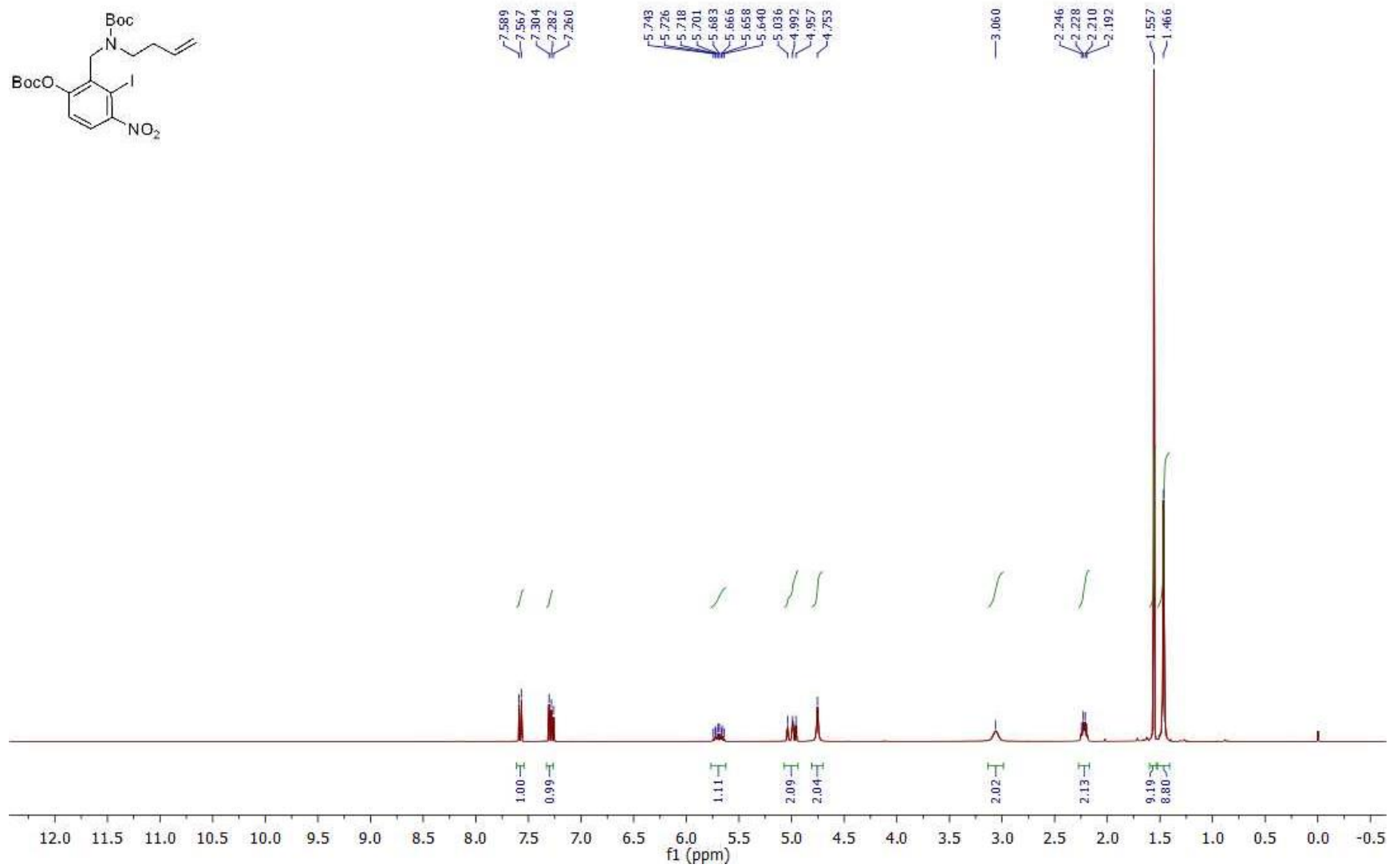


Figure 11: ¹H NMR of Compound 97

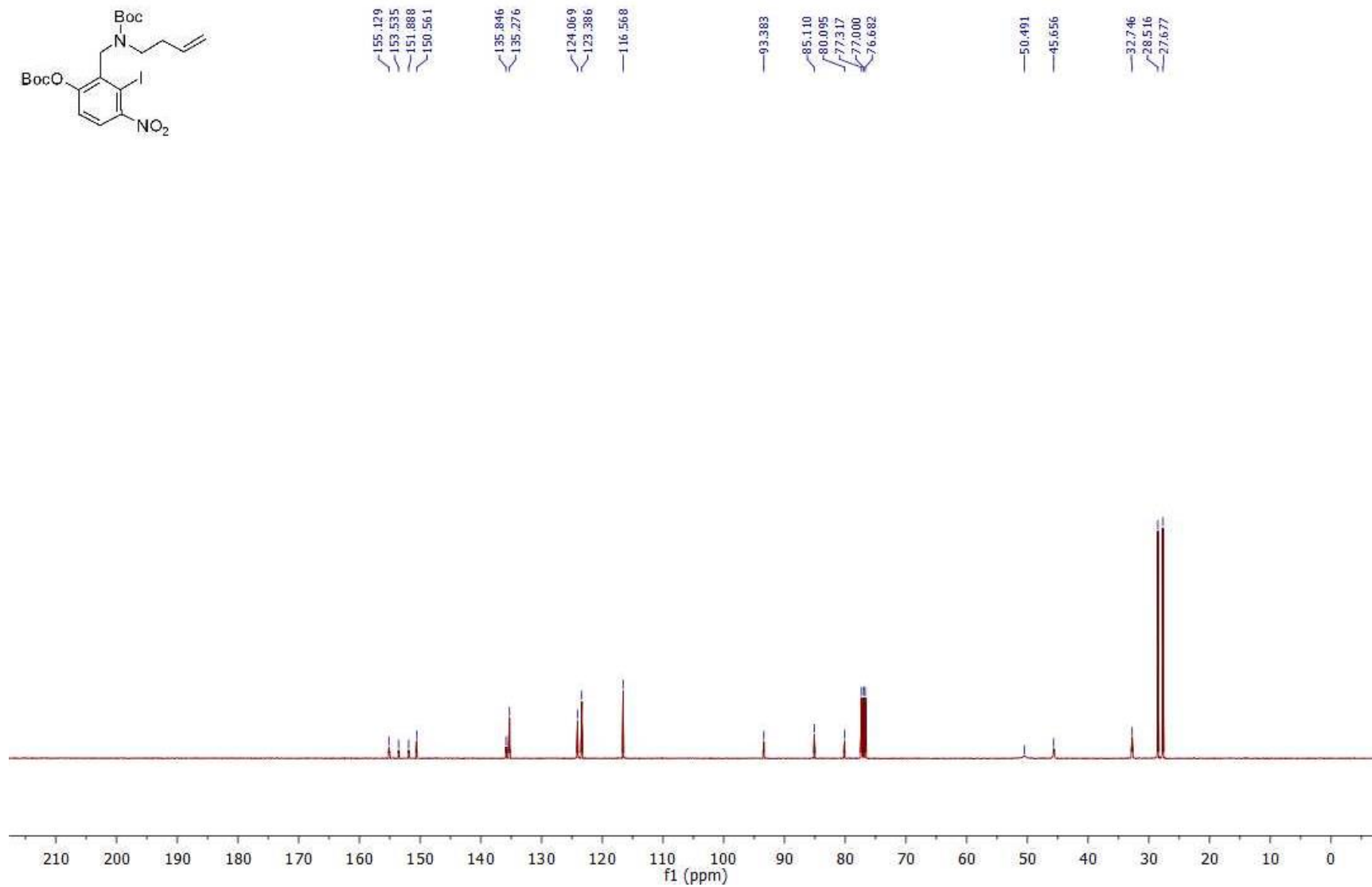


Figure 12: ^{13}C NMR of Compound **97**

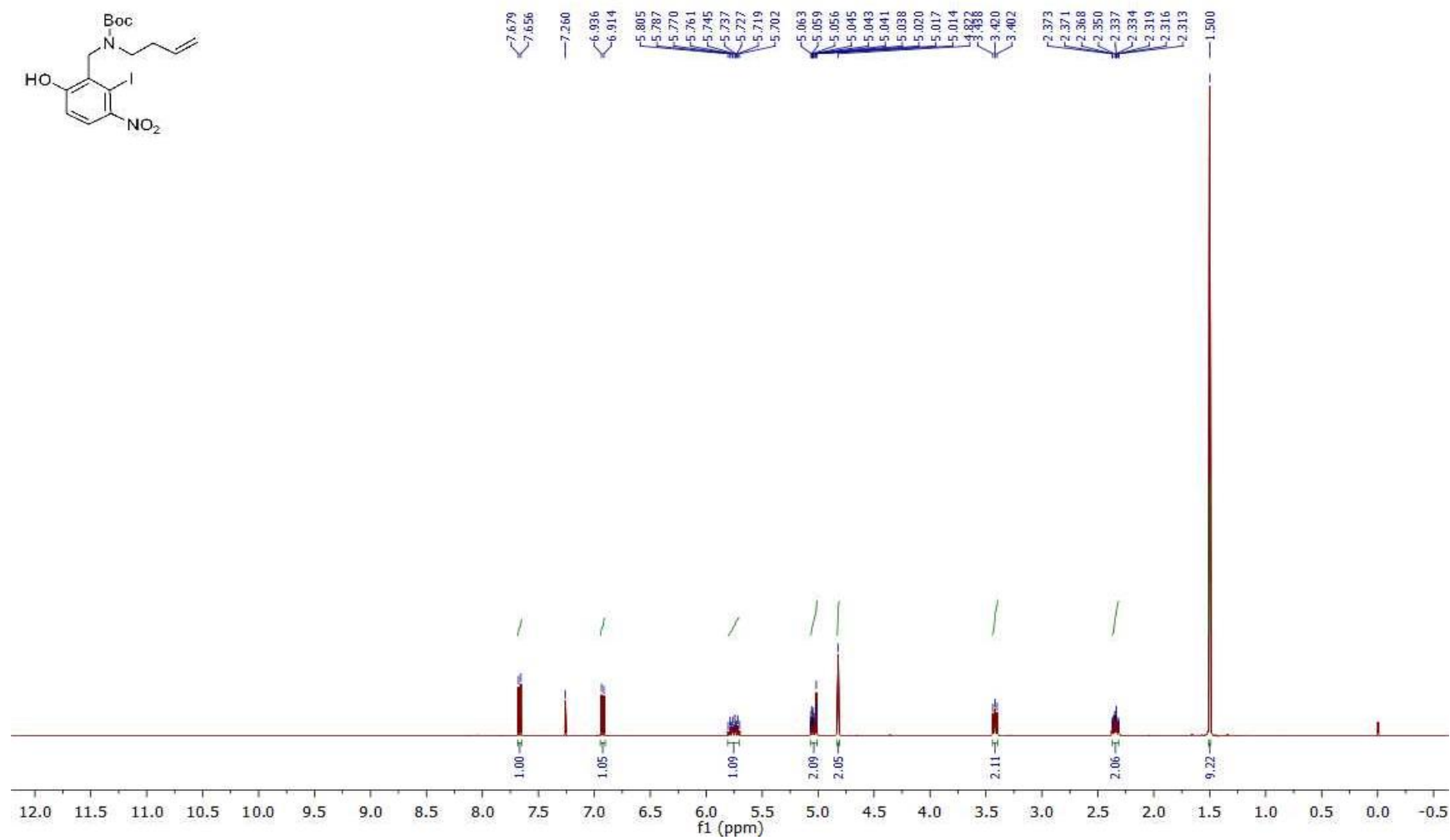


Figure 13: ¹H NMR of Compound **98**

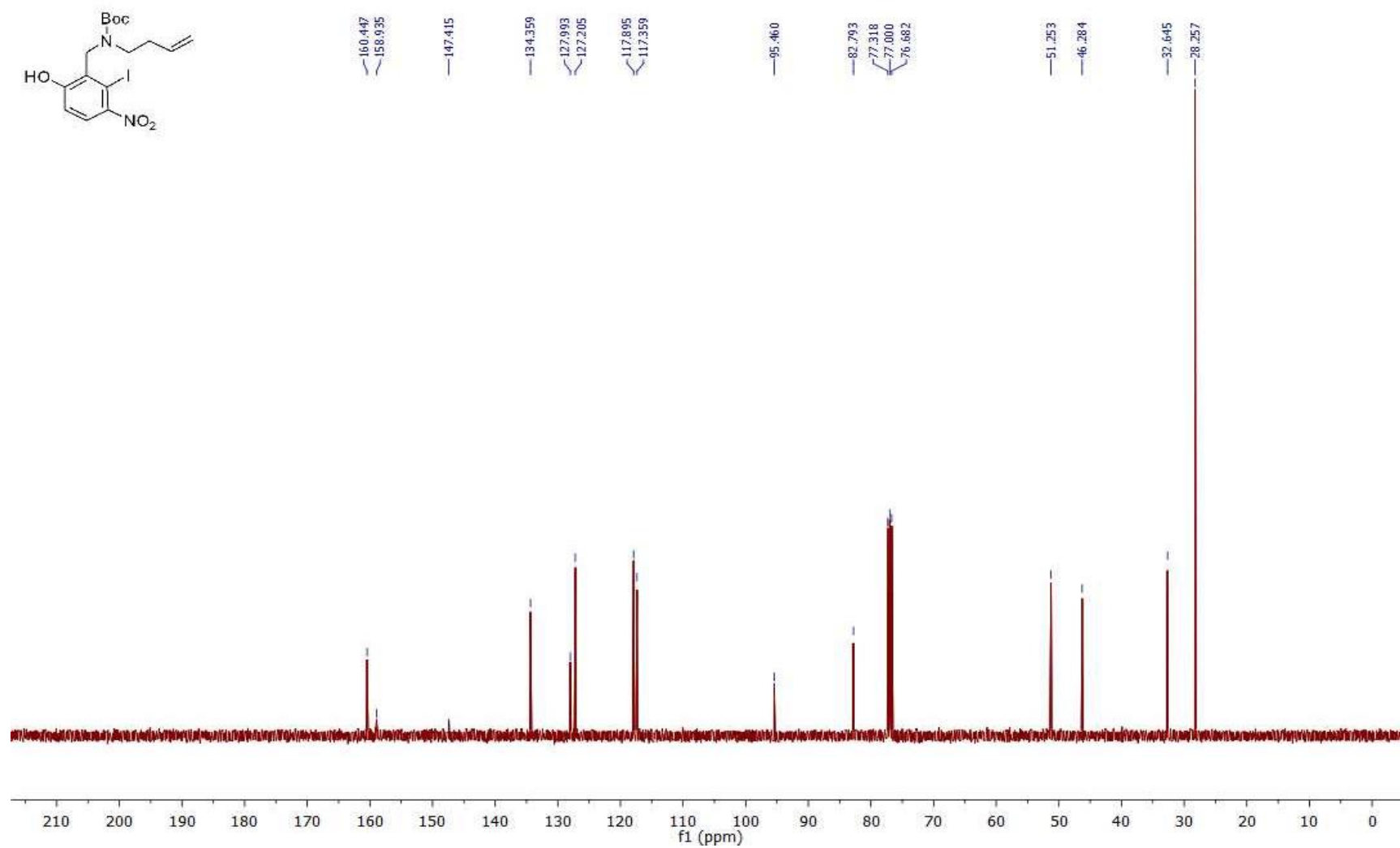
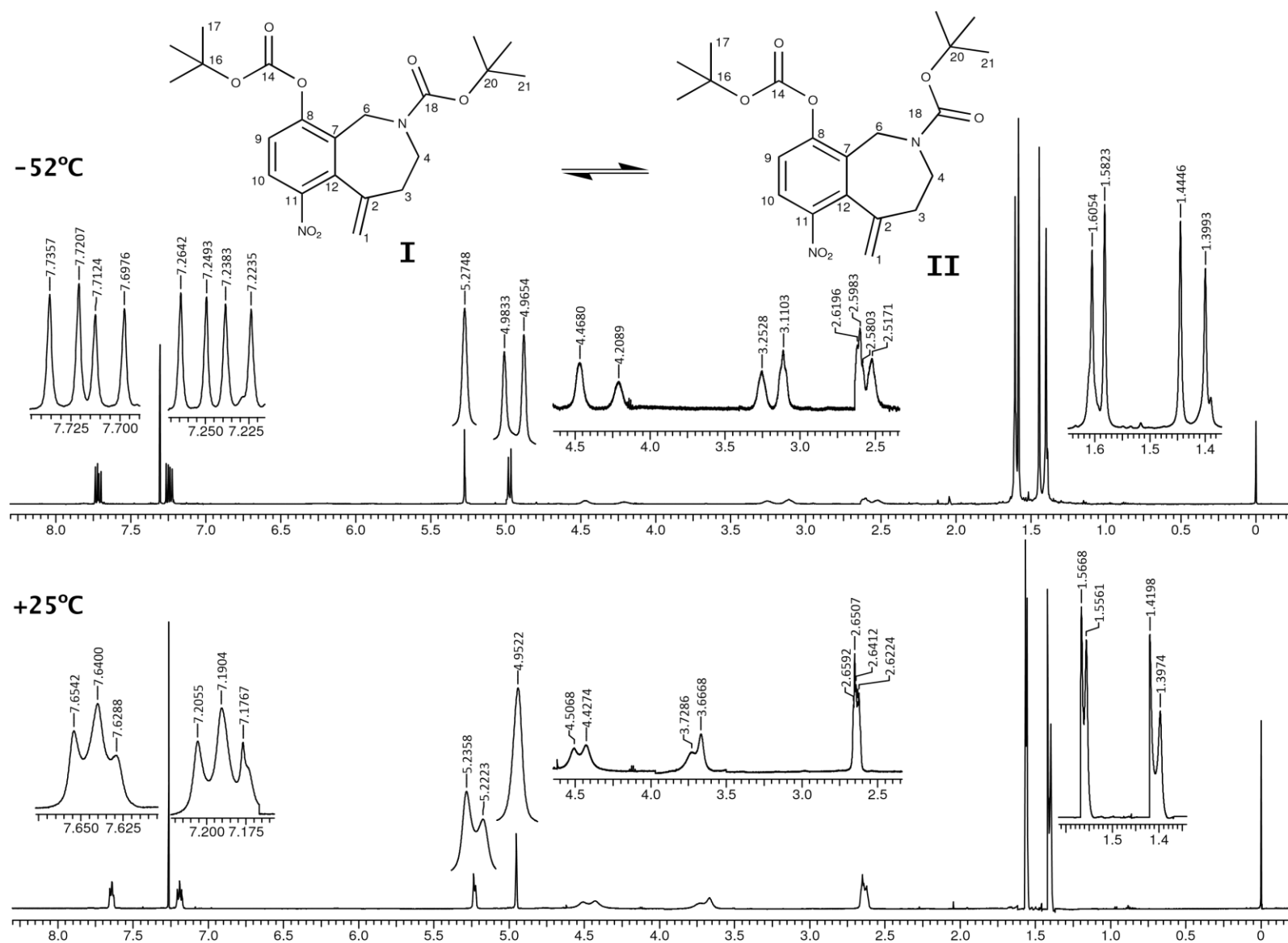


Figure 14: ^{13}C NMR of Compound **98**



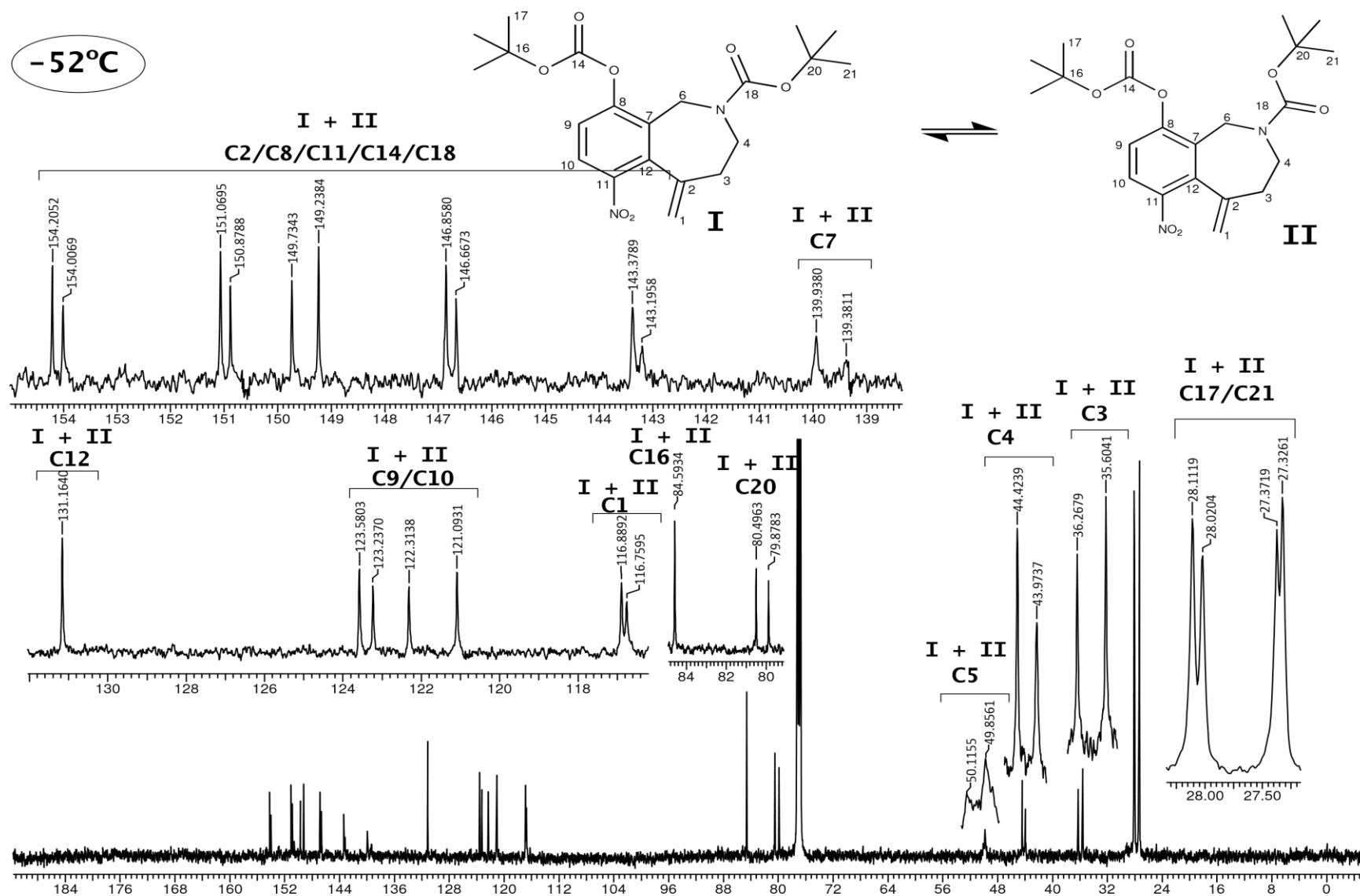


Figure 16: ^{13}C NMR of Compound **101**

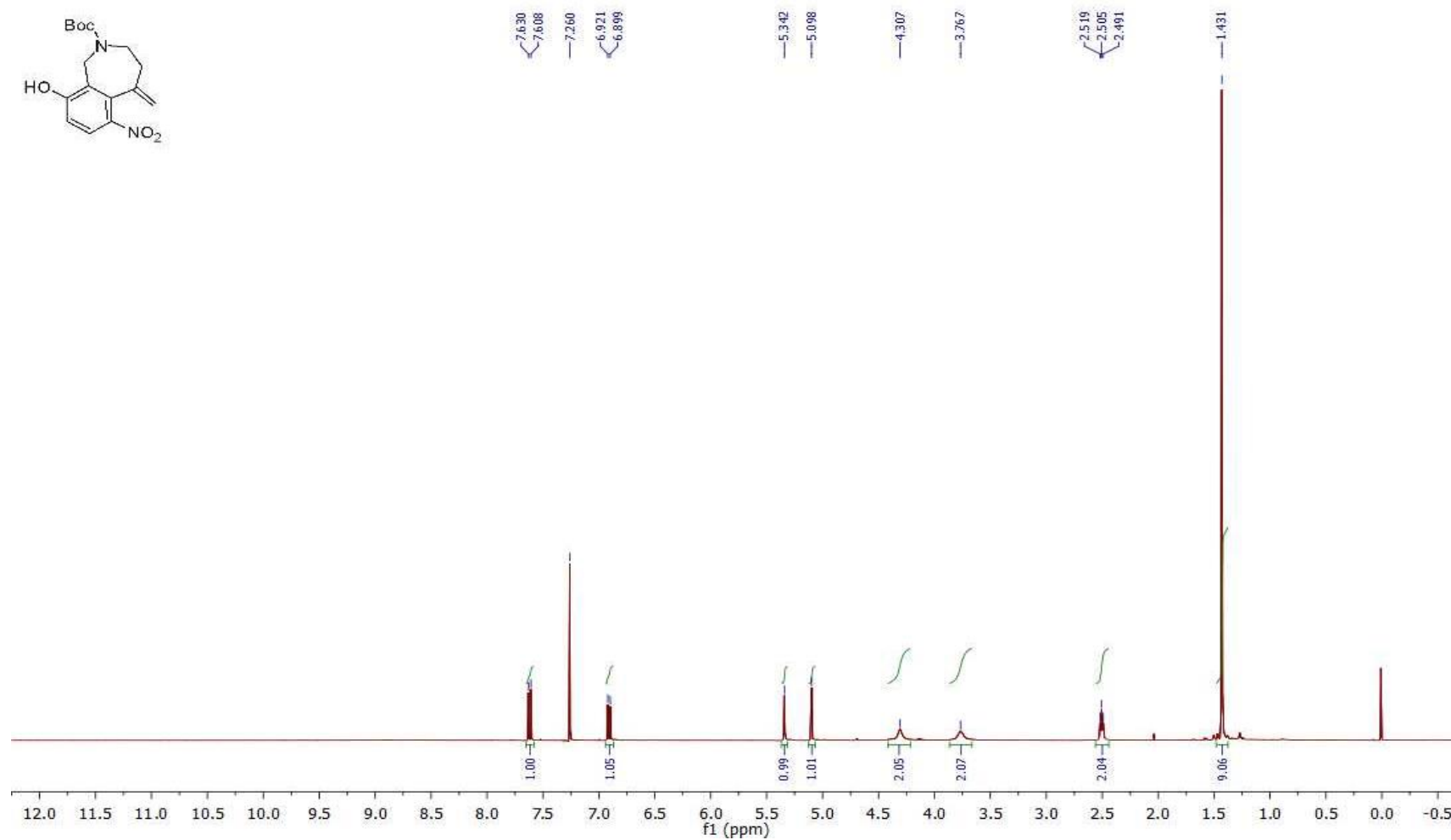


Figure 17: ¹H NMR of Compound **102**

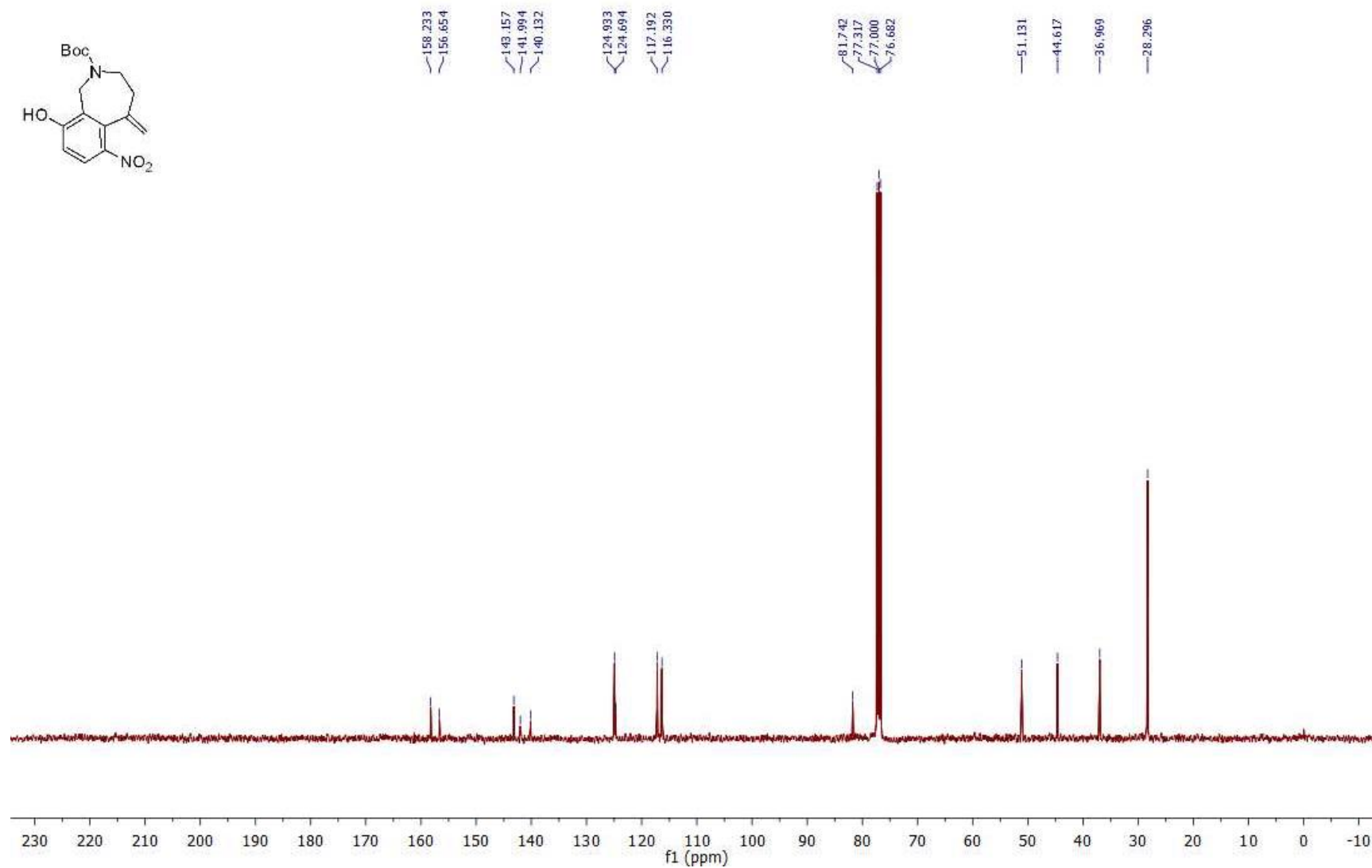


Figure 18: ¹³C NMR of Compound **102**

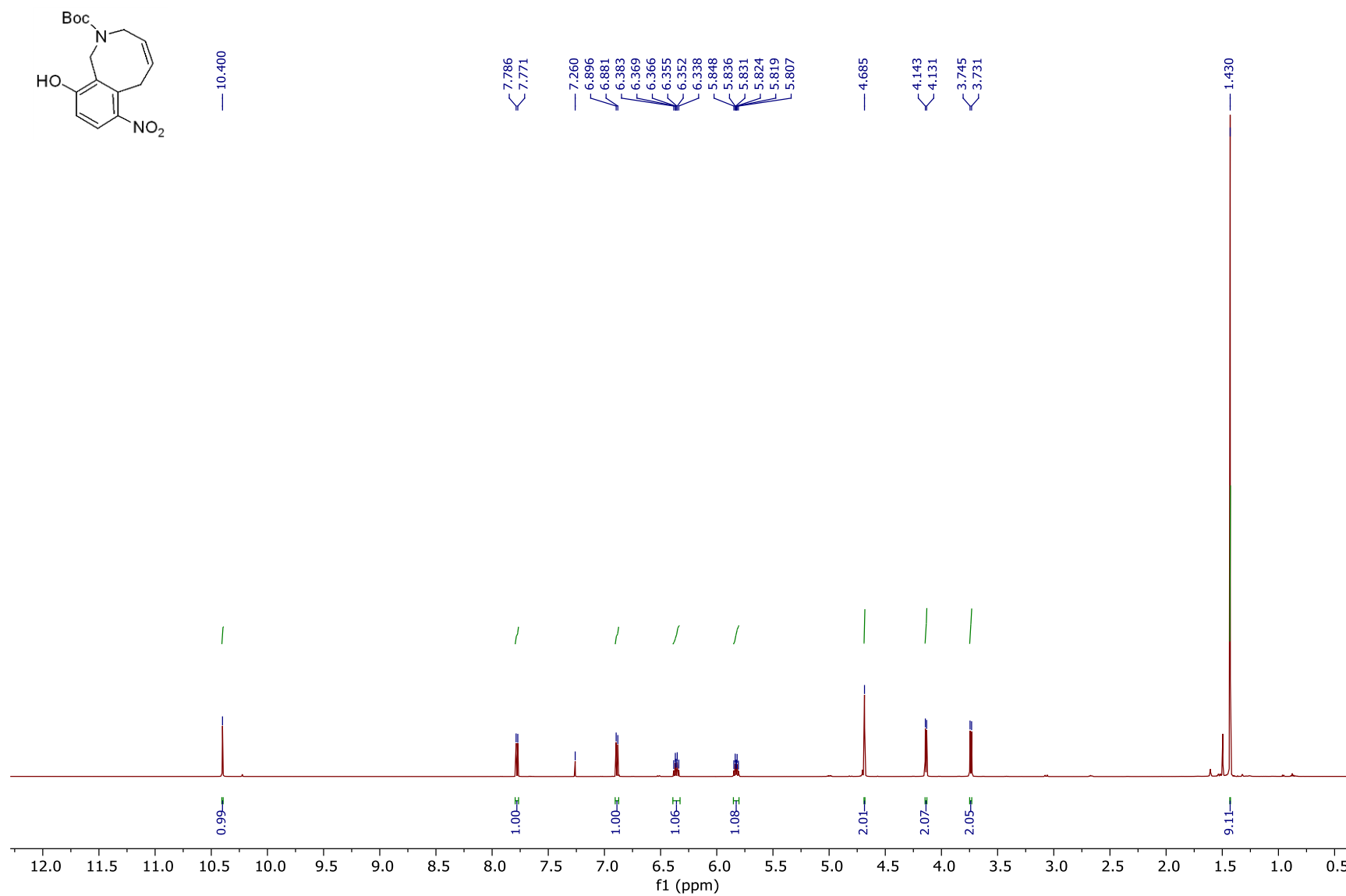


Figure 19: ¹H NMR of Compound **103**

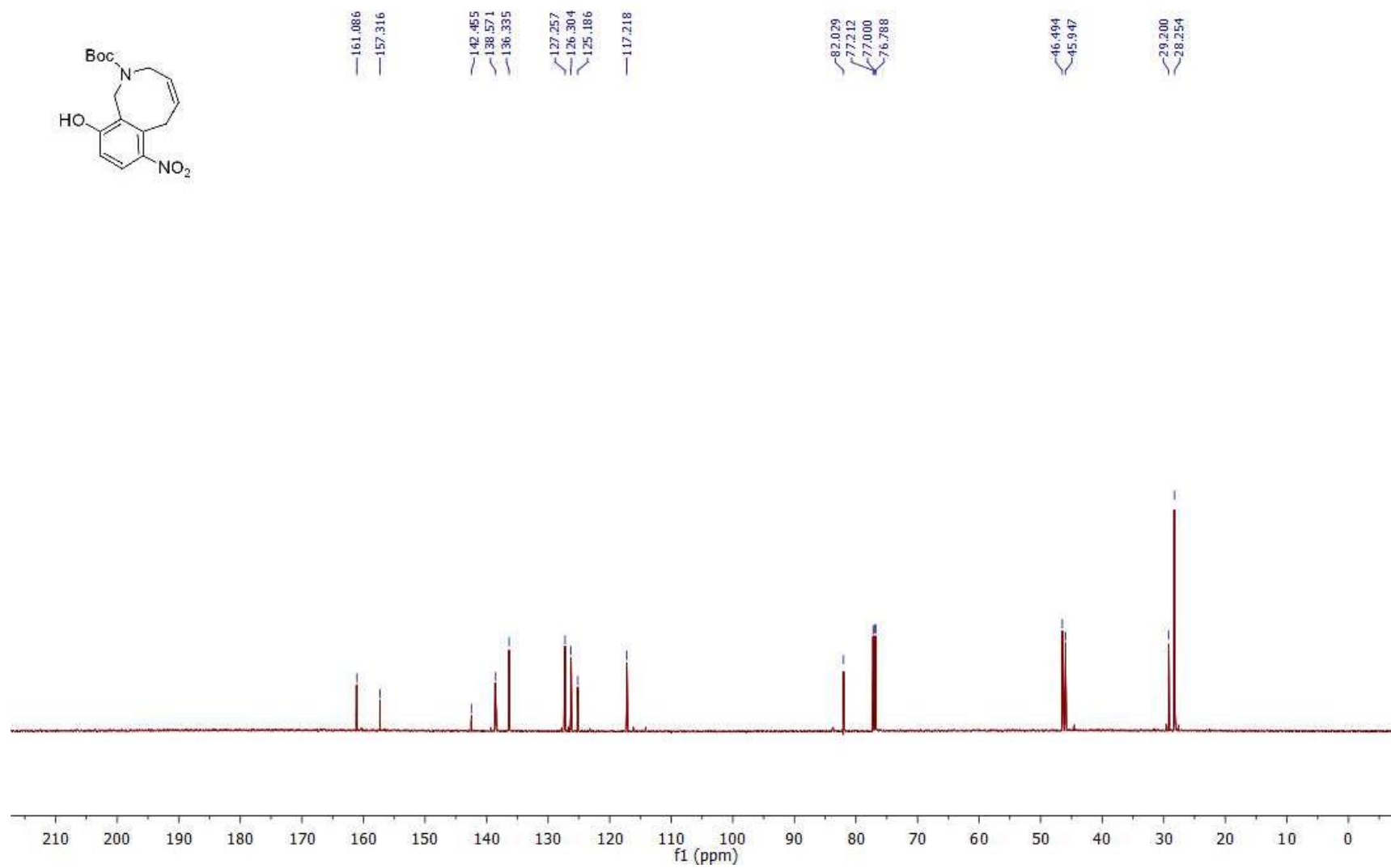


Figure 20: ^{13}C NMR of Compound **103**

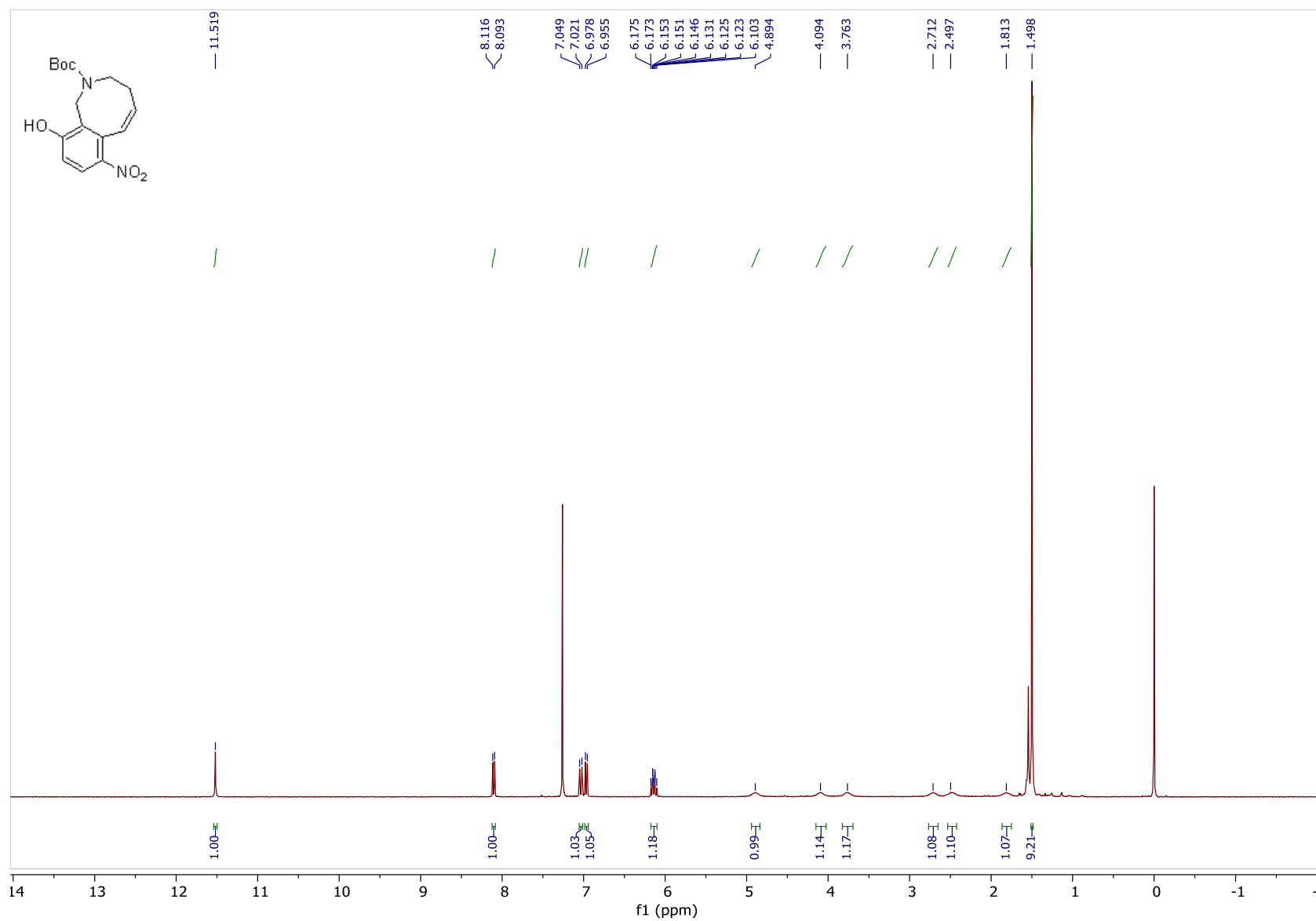


Figure 21: ¹H NMR of Compound **104**

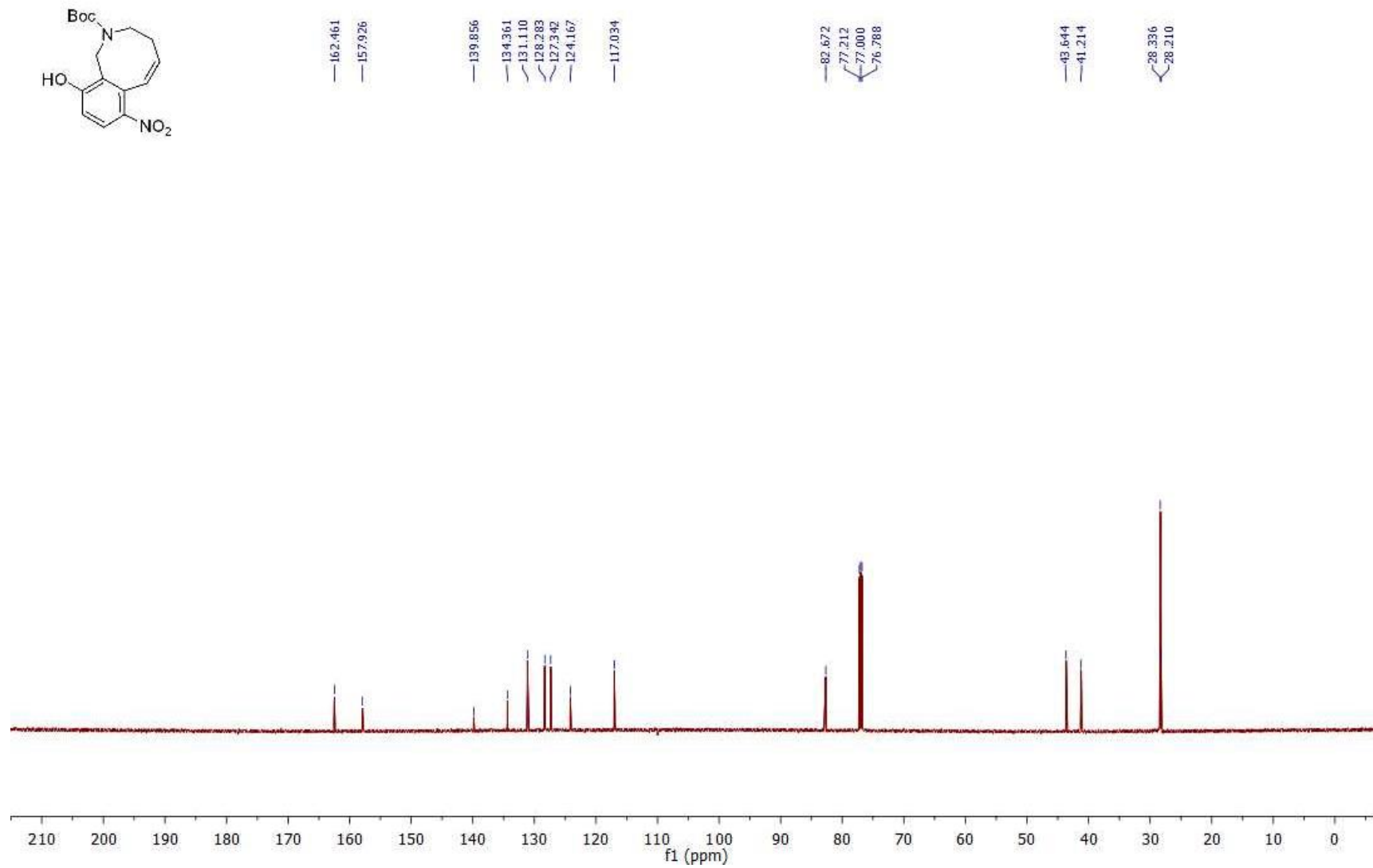


Figure 22: ^{13}C NMR of Compound **104**

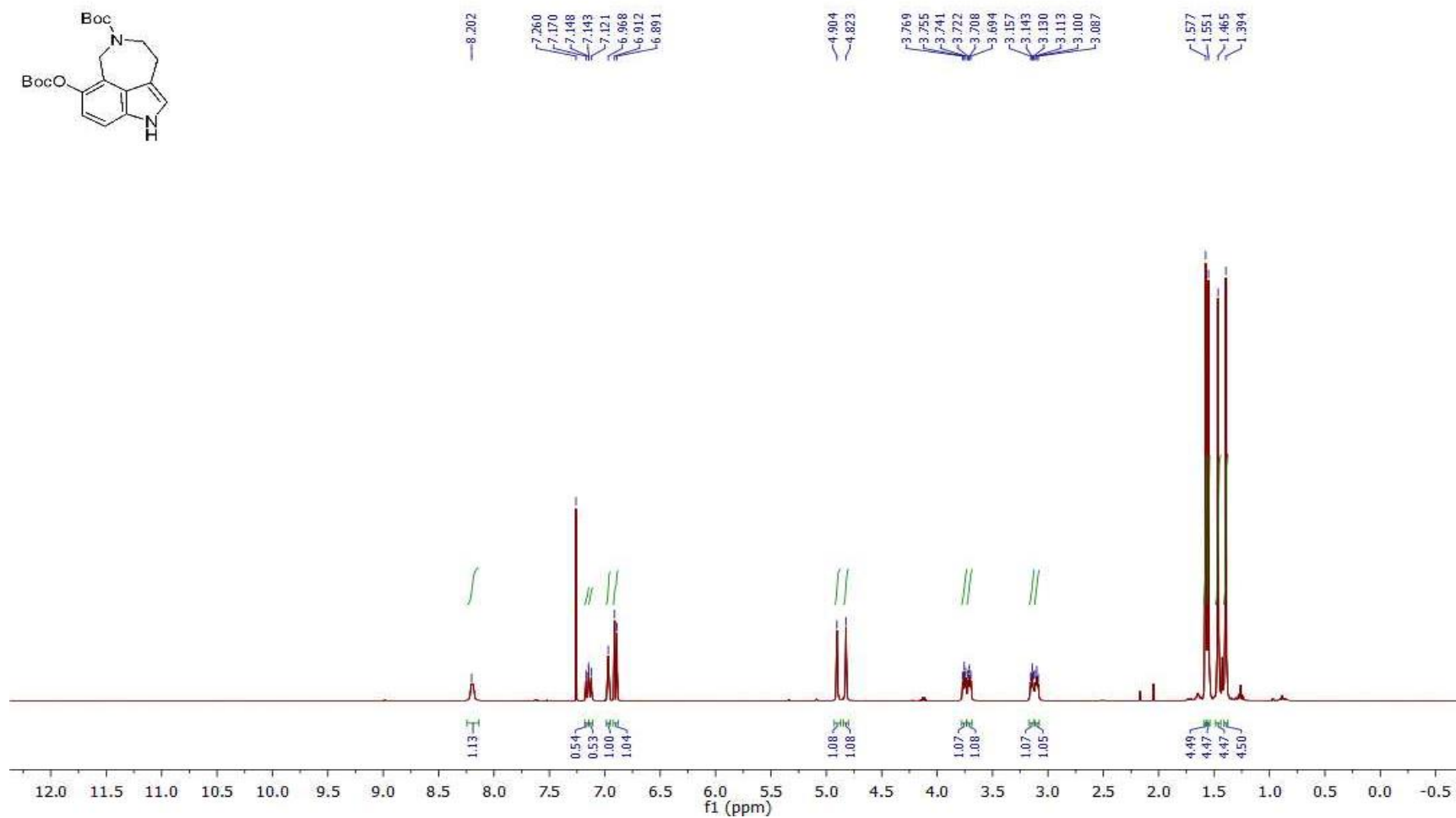


Figure 23: ^1H NMR of Compound **105**

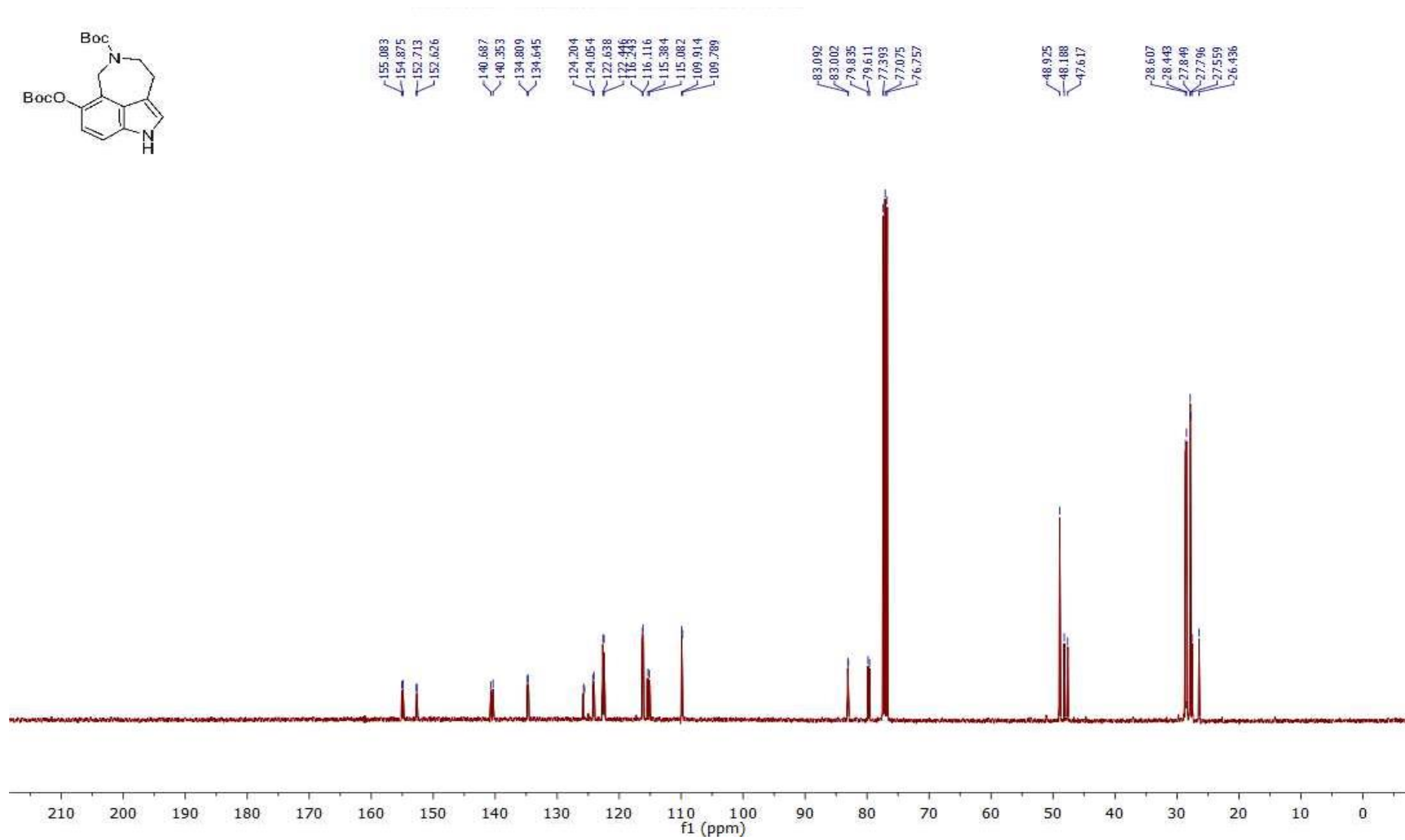


Figure 24: ^{13}C NMR of Compound **105**

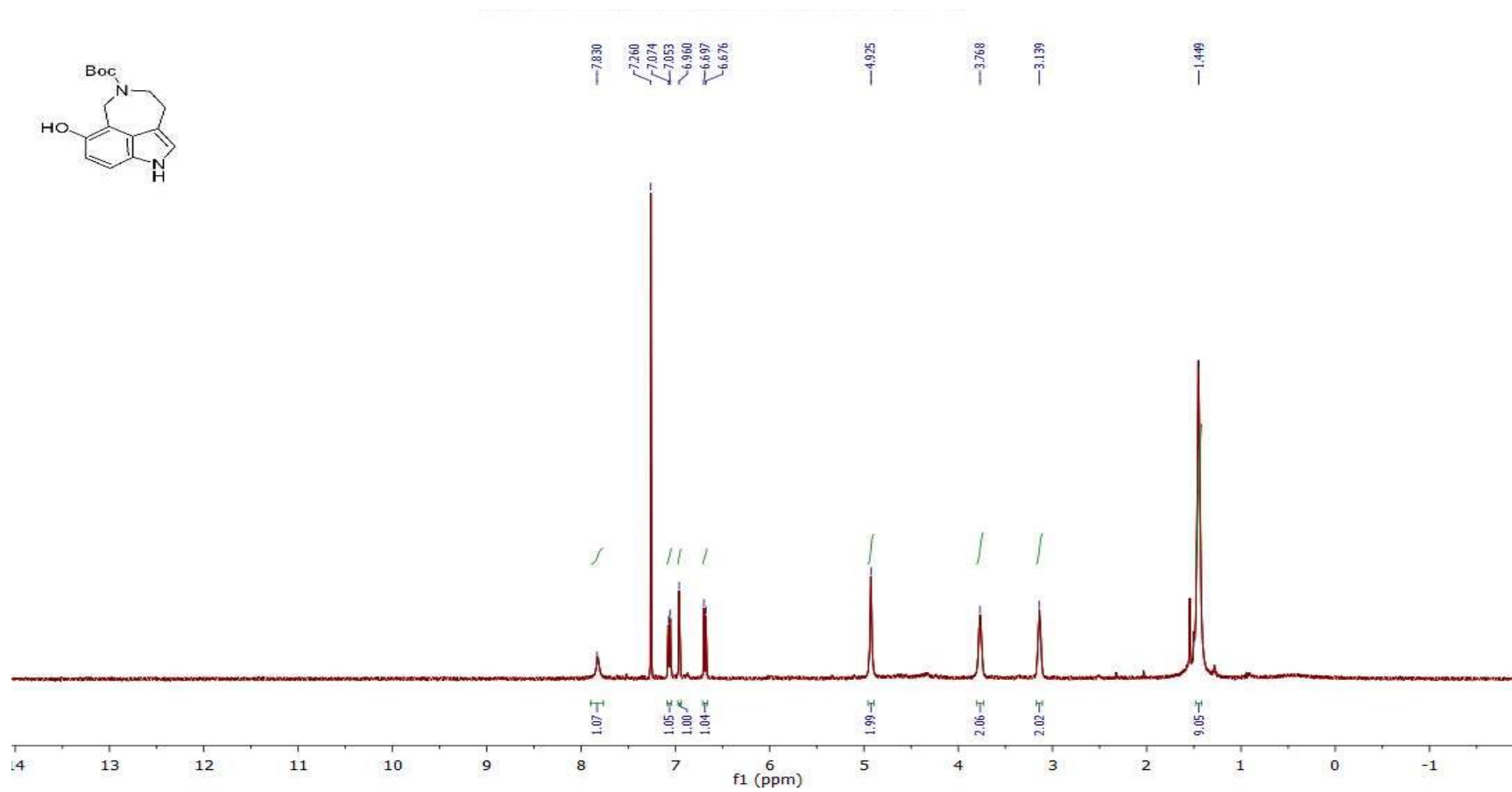


Figure 25: ^1H NMR of Compound **106**

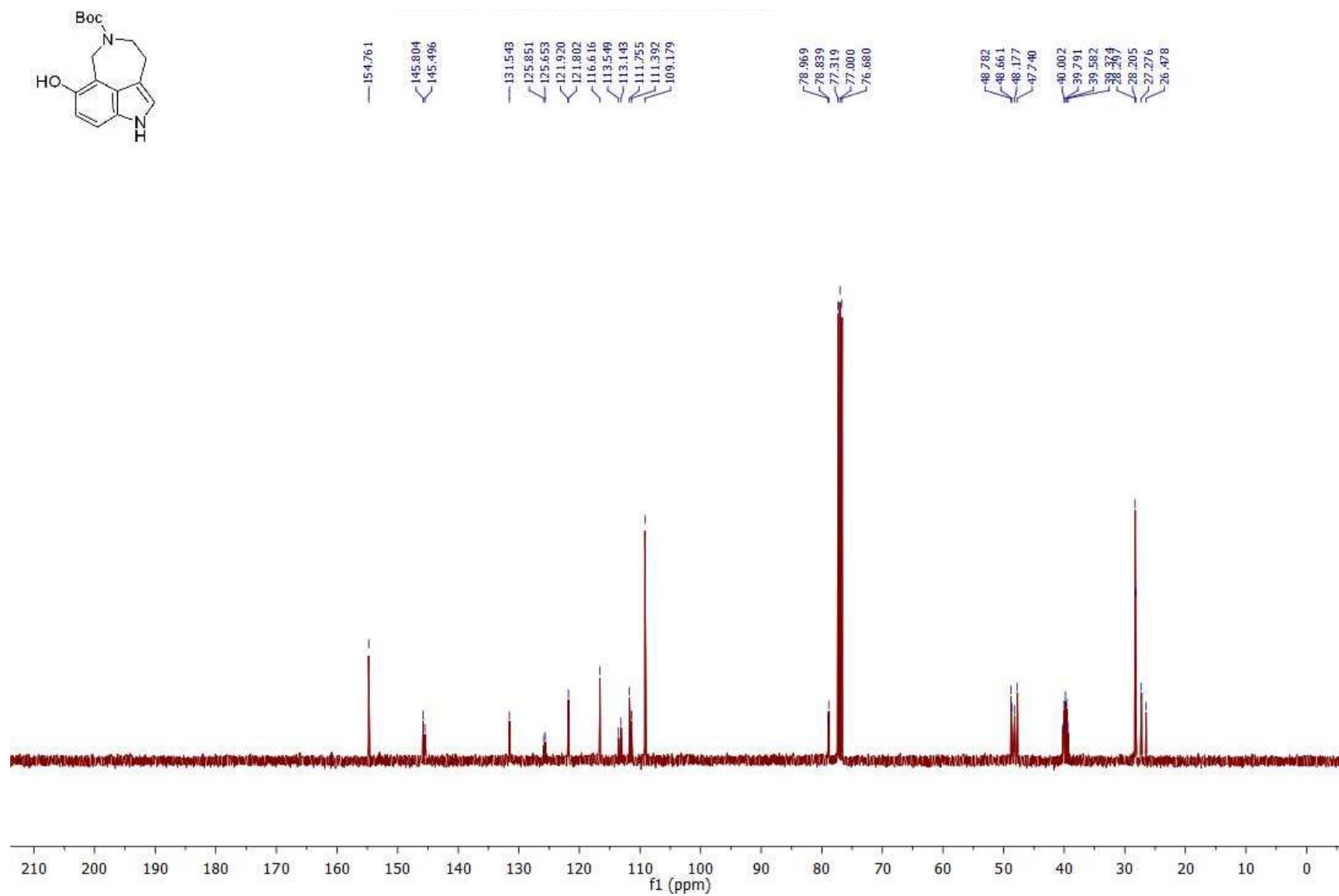


Figure 26: ^{13}C NMR of Compound **106**

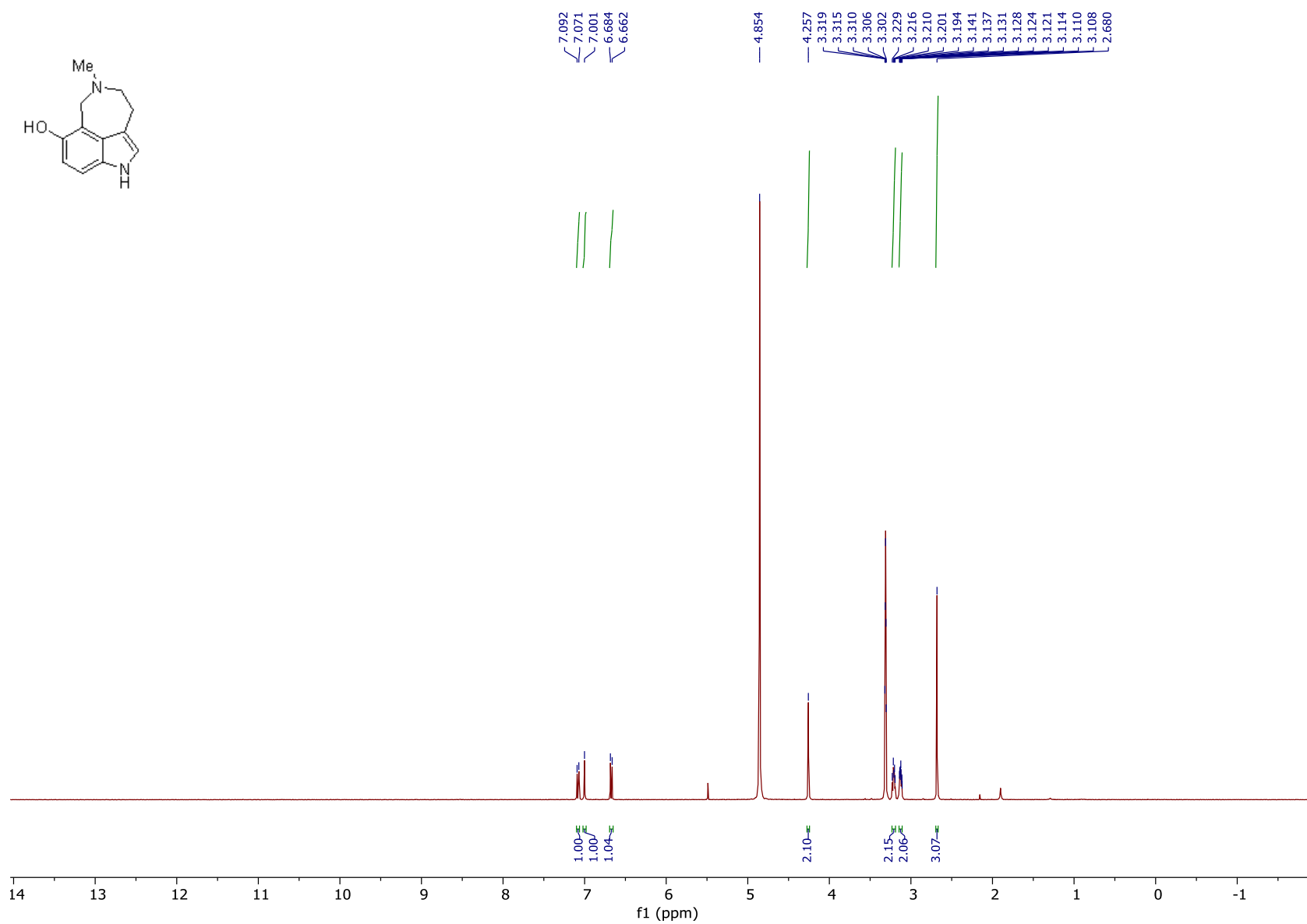


Figure 27: ¹H NMR of Compound **88**

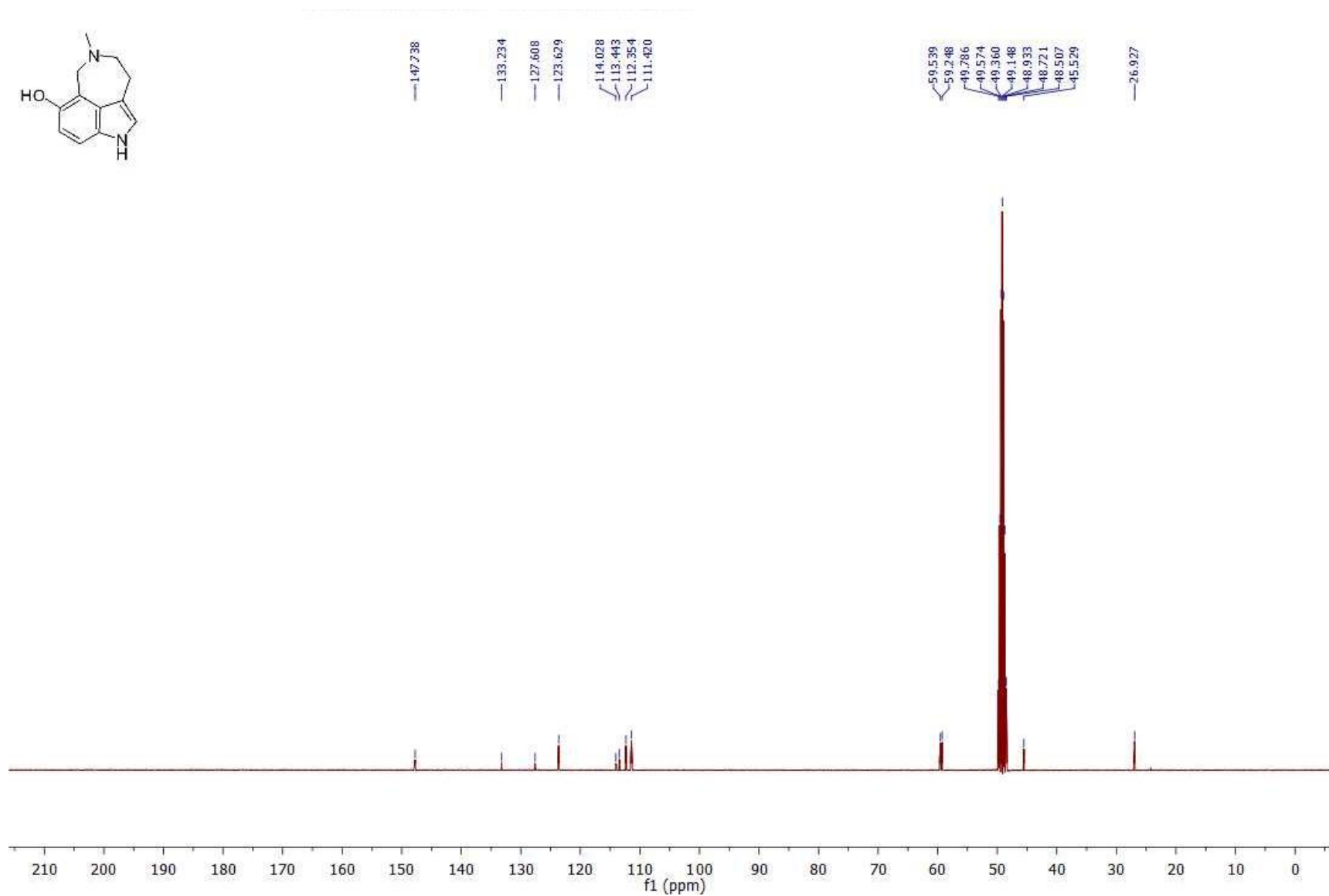


Figure 28: ^{13}C NMR of Compound **88**

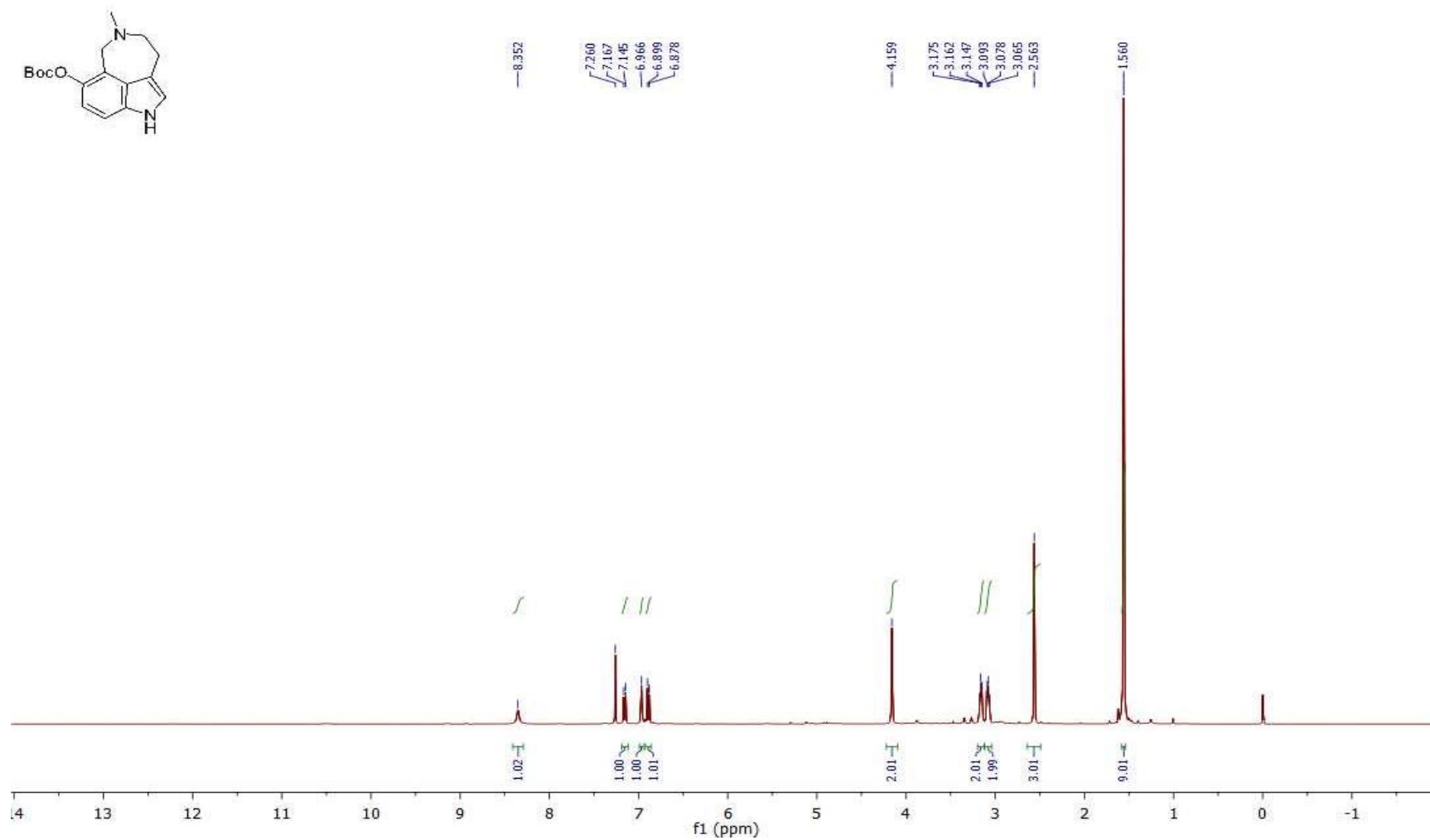


Figure 29: ^1H NMR of Compound **107**

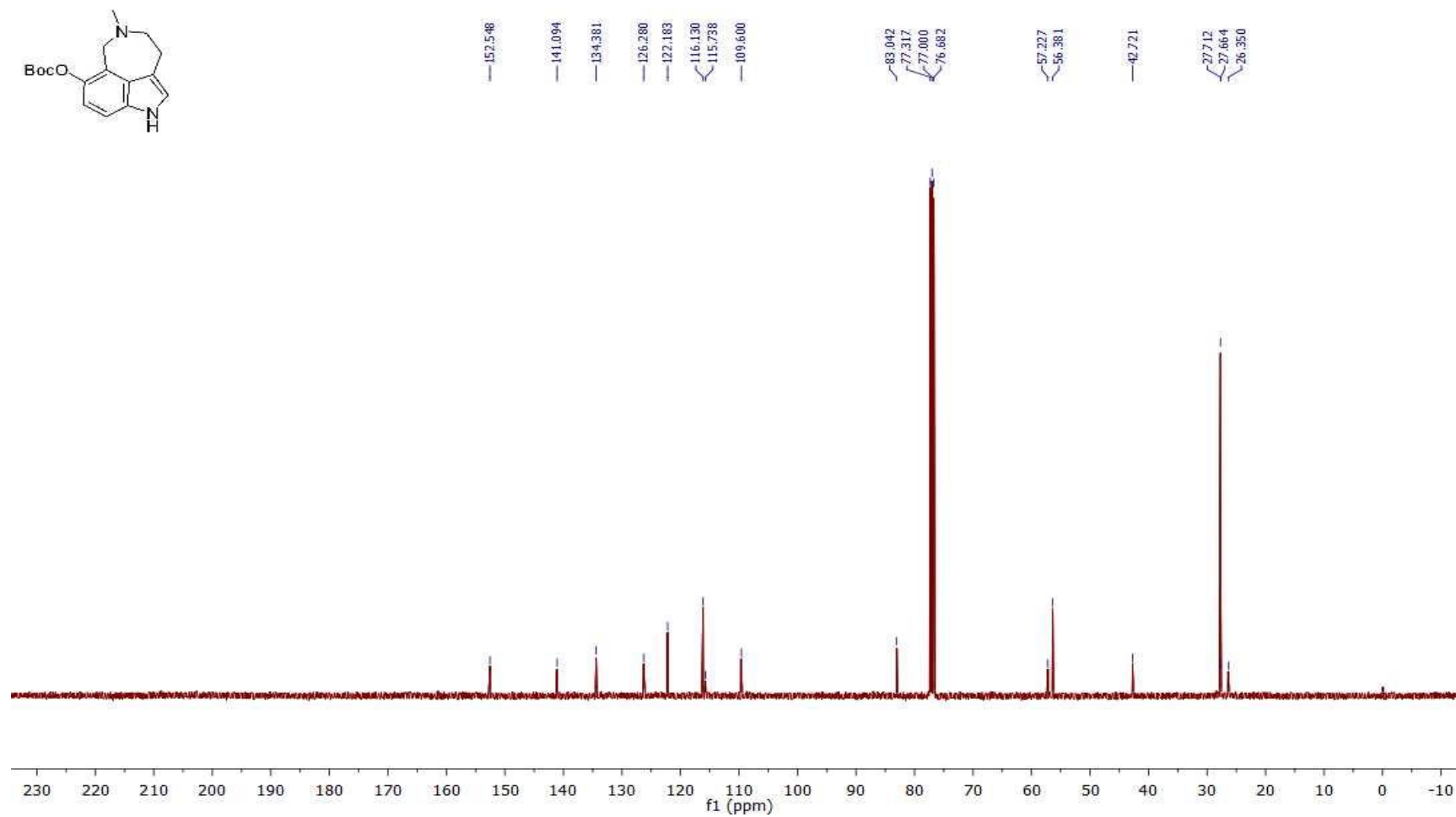


Figure 30: ^{13}C NMR of Compound **107**

¹H and ¹³C NMR for Chapter 3: Hyrtioreticulins C & D

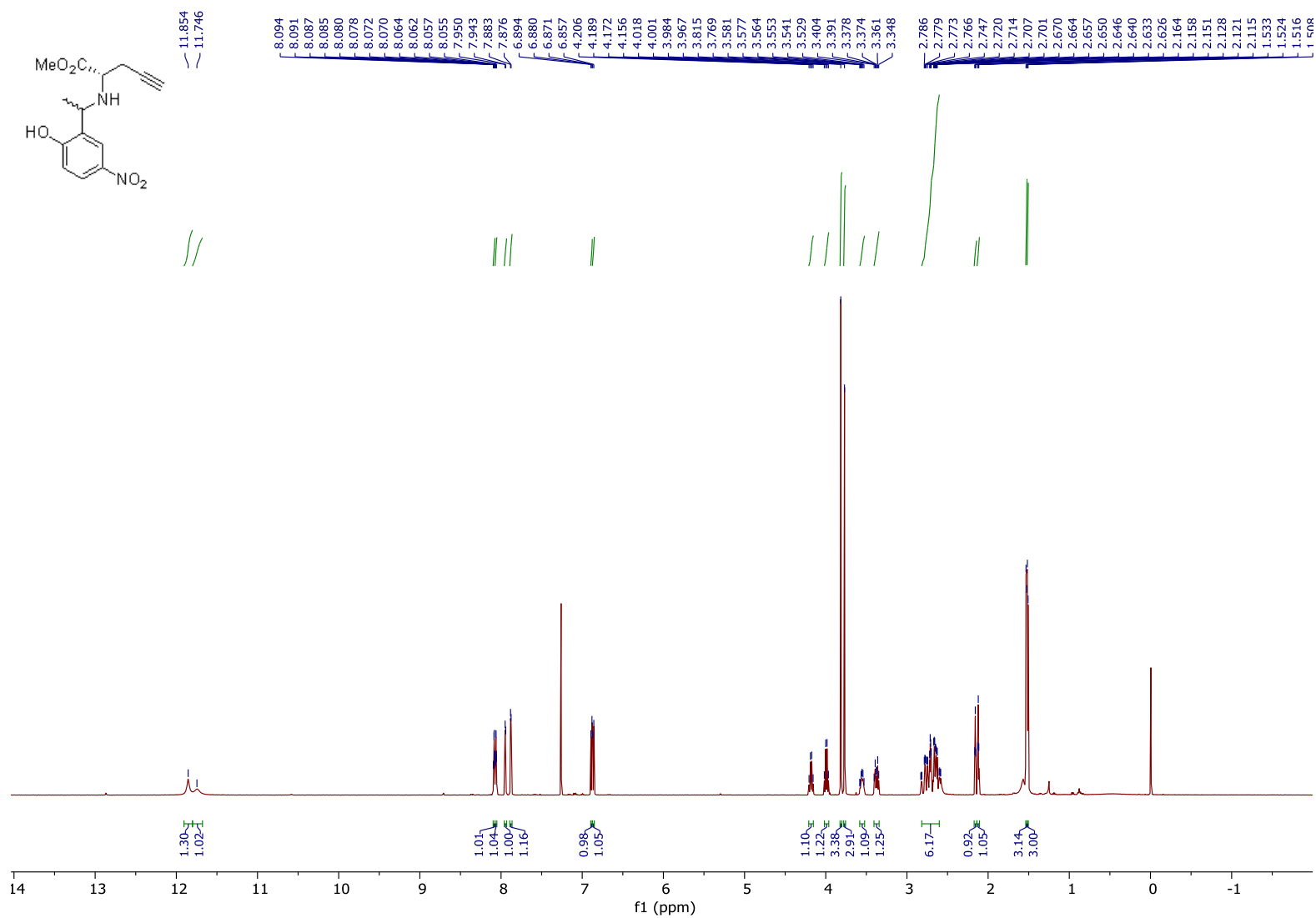


Figure 31: ¹H NMR of Compound 127

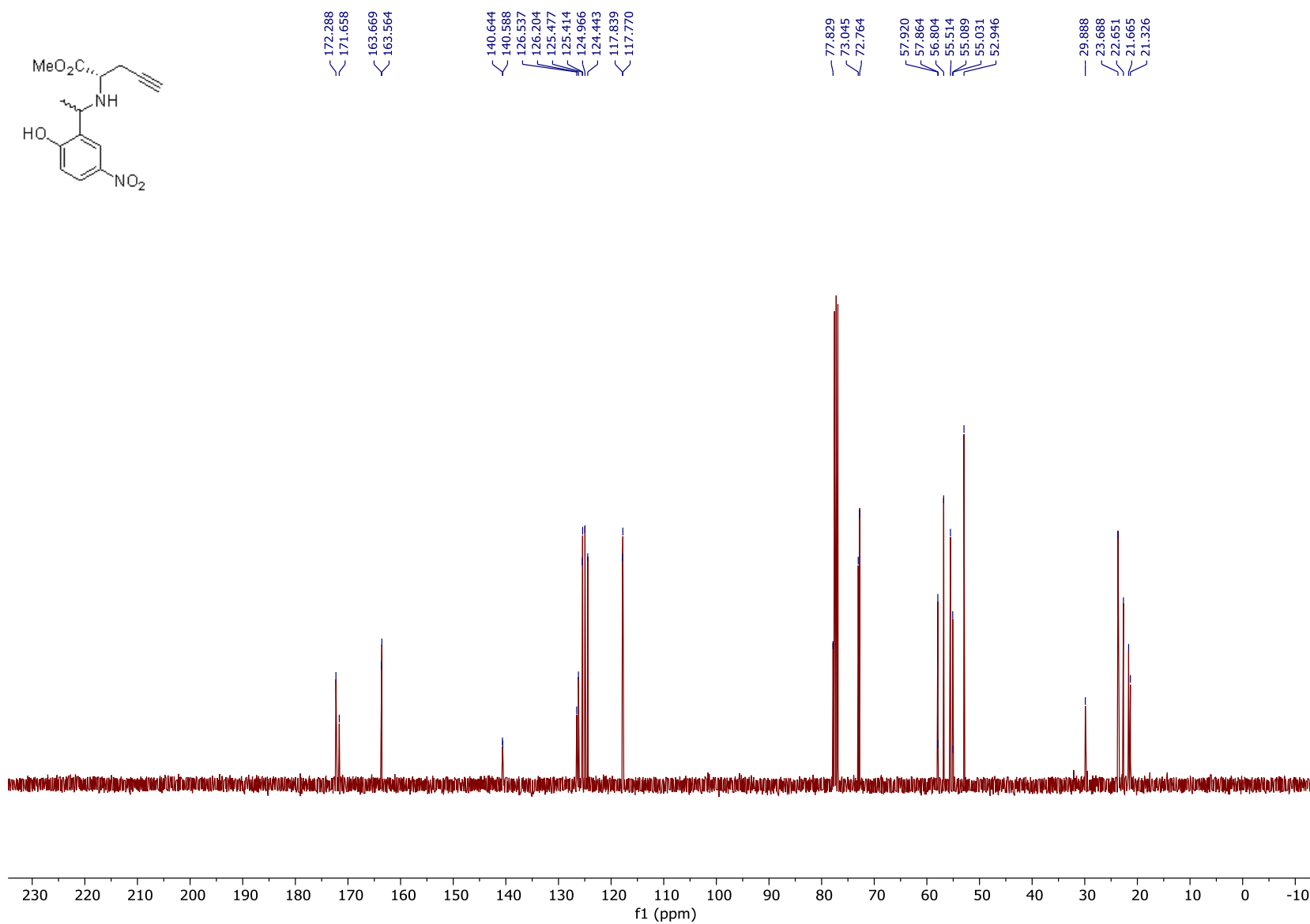


Figure 32: ^{13}C NMR of Compound **127**

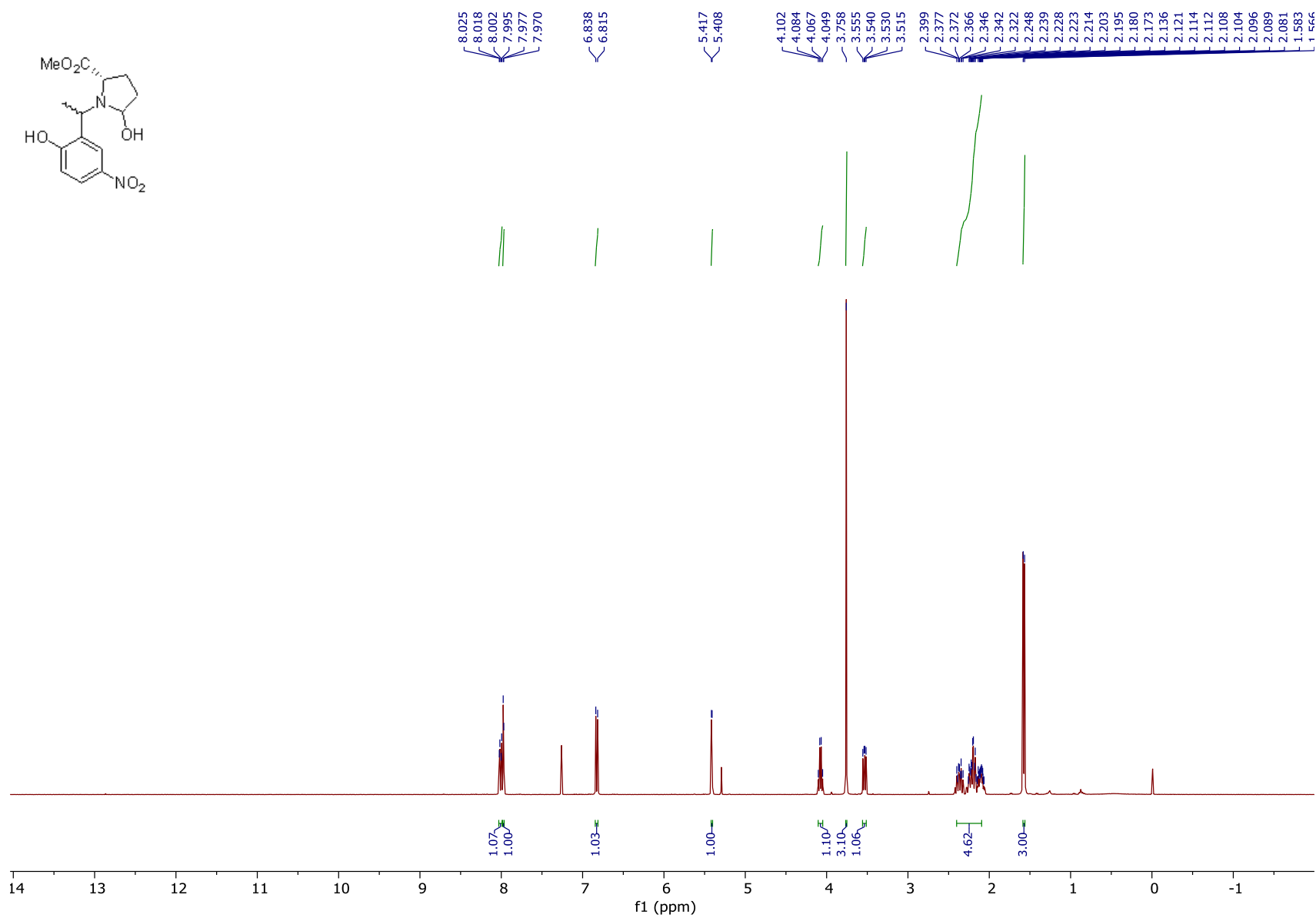


Figure 33: ¹H NMR of Compound **128**

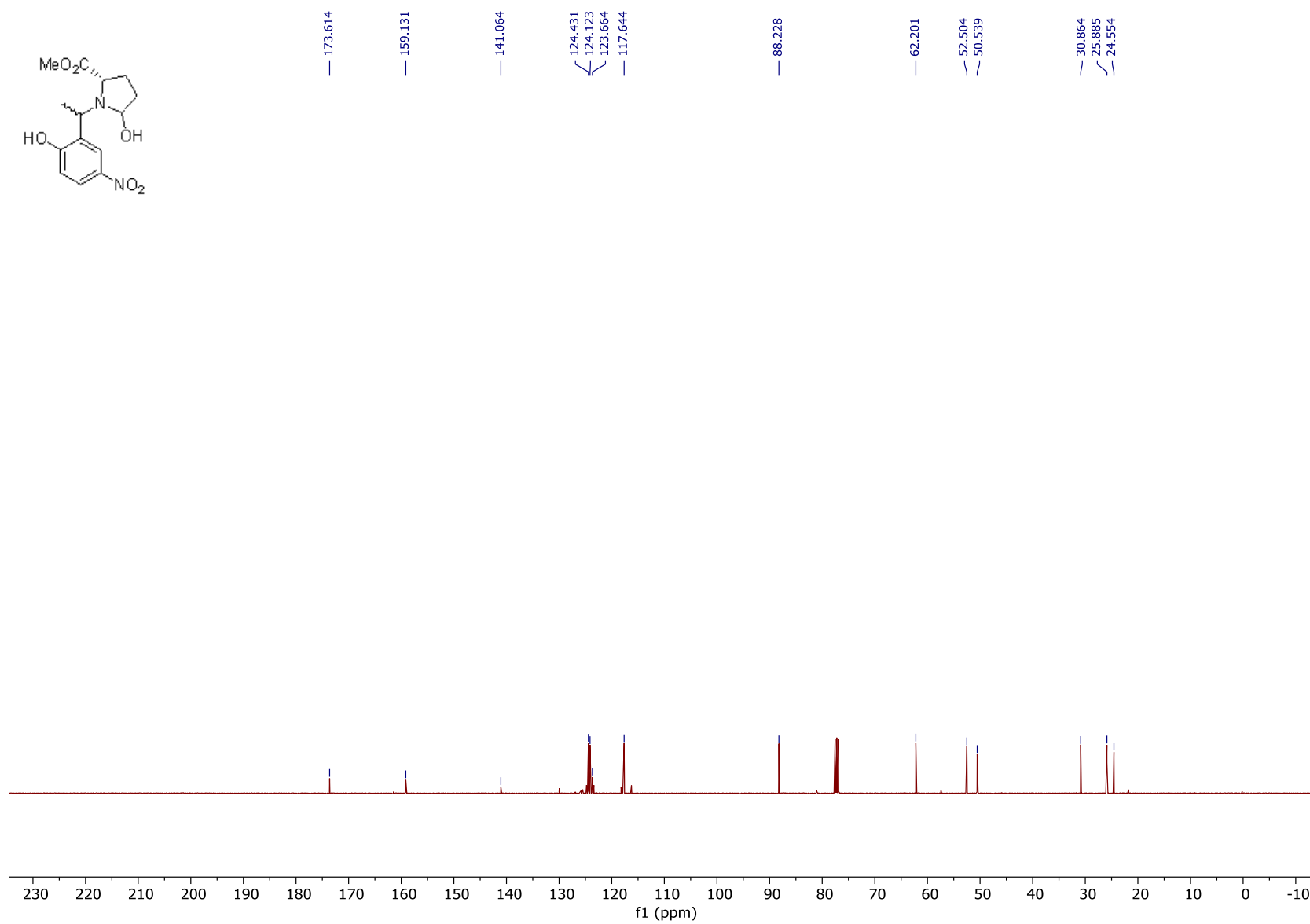


Figure 34: ¹³C NMR of Compound **128**

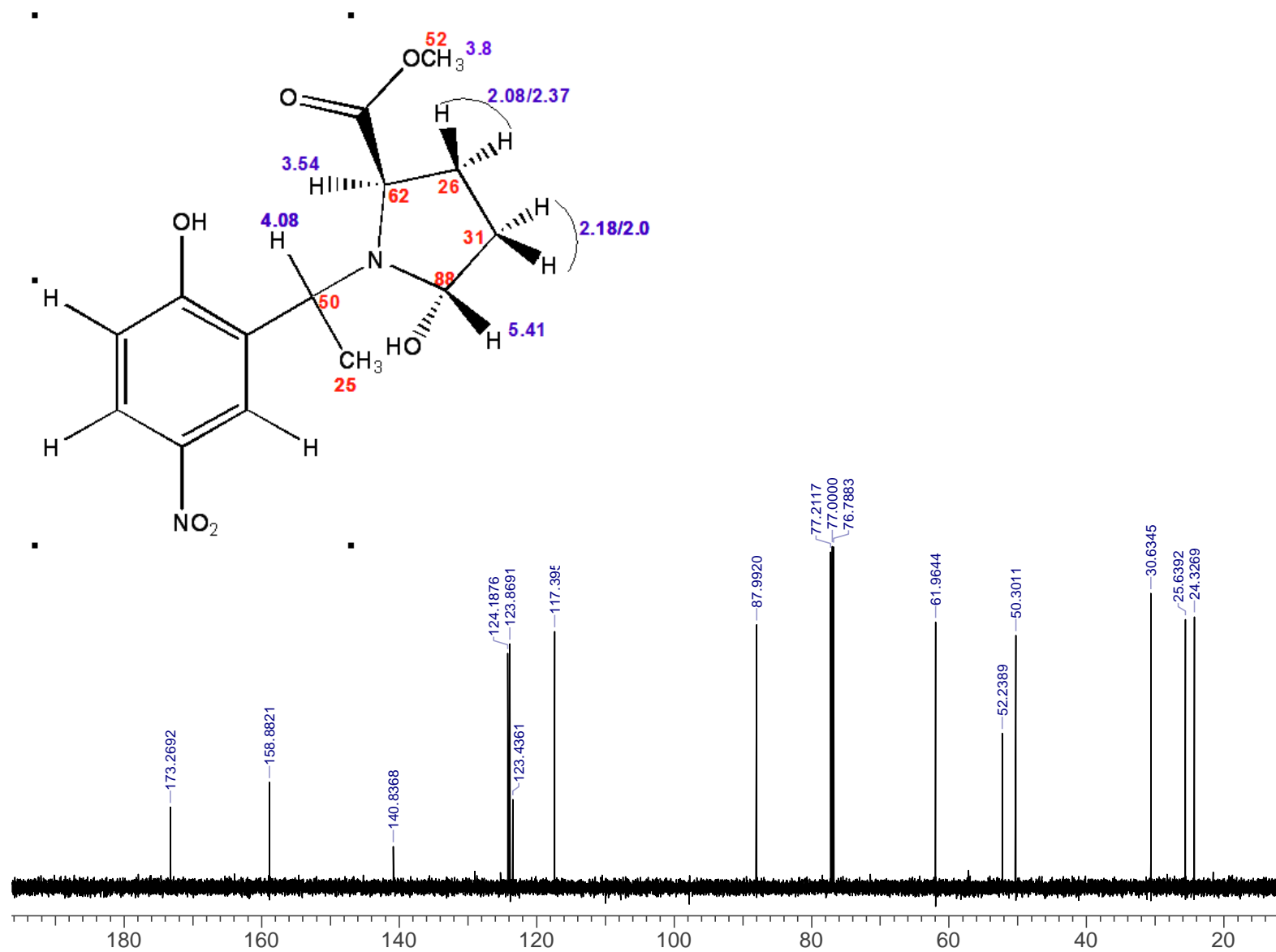


Figure 35: ¹³C NMR of Compound 128

gCOSY

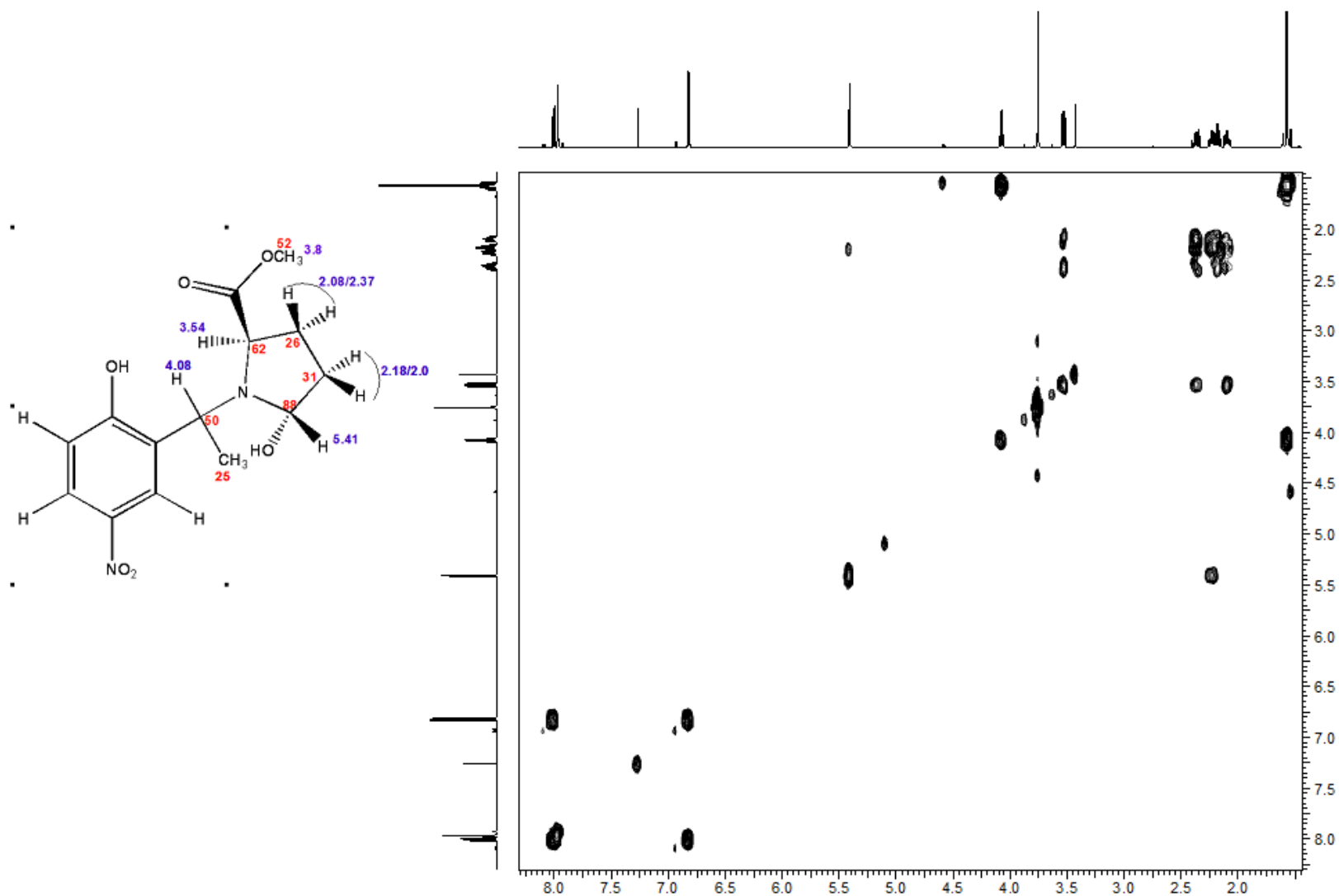


Figure 36: COSY of Compound 128

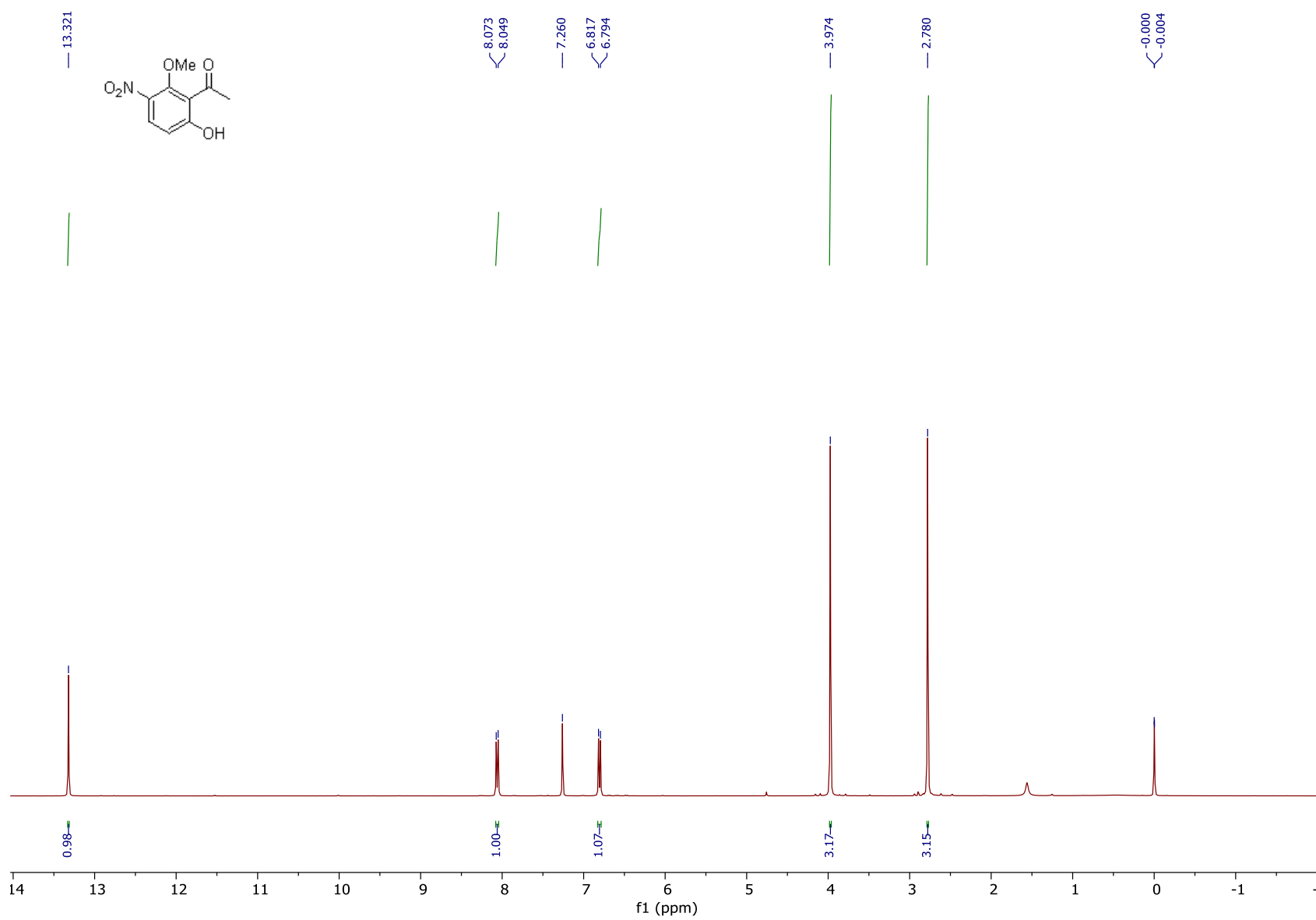


Figure 37: ¹H NMR of Compound **136**

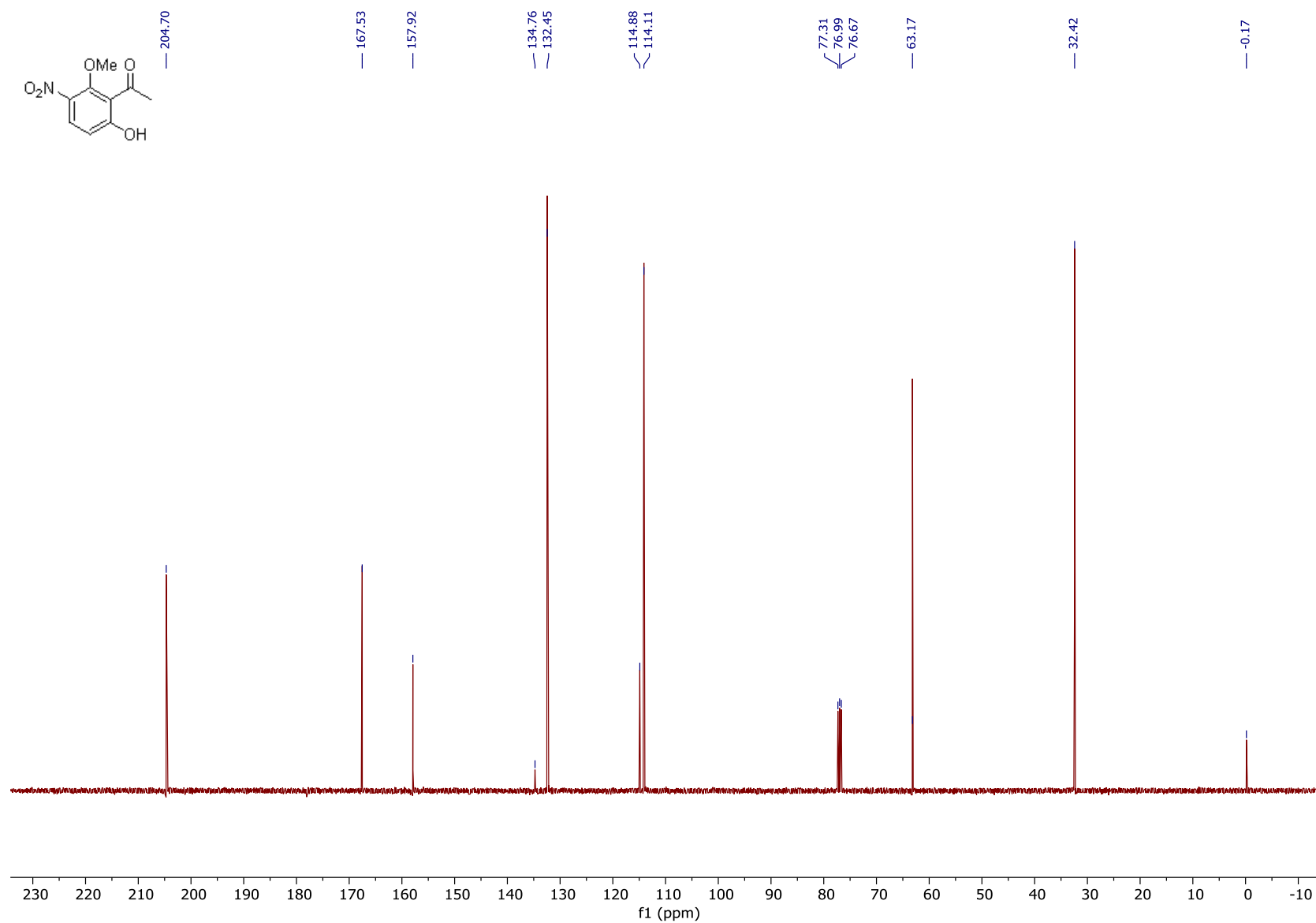


Figure 38: ^{13}C NMR of Compound **136**

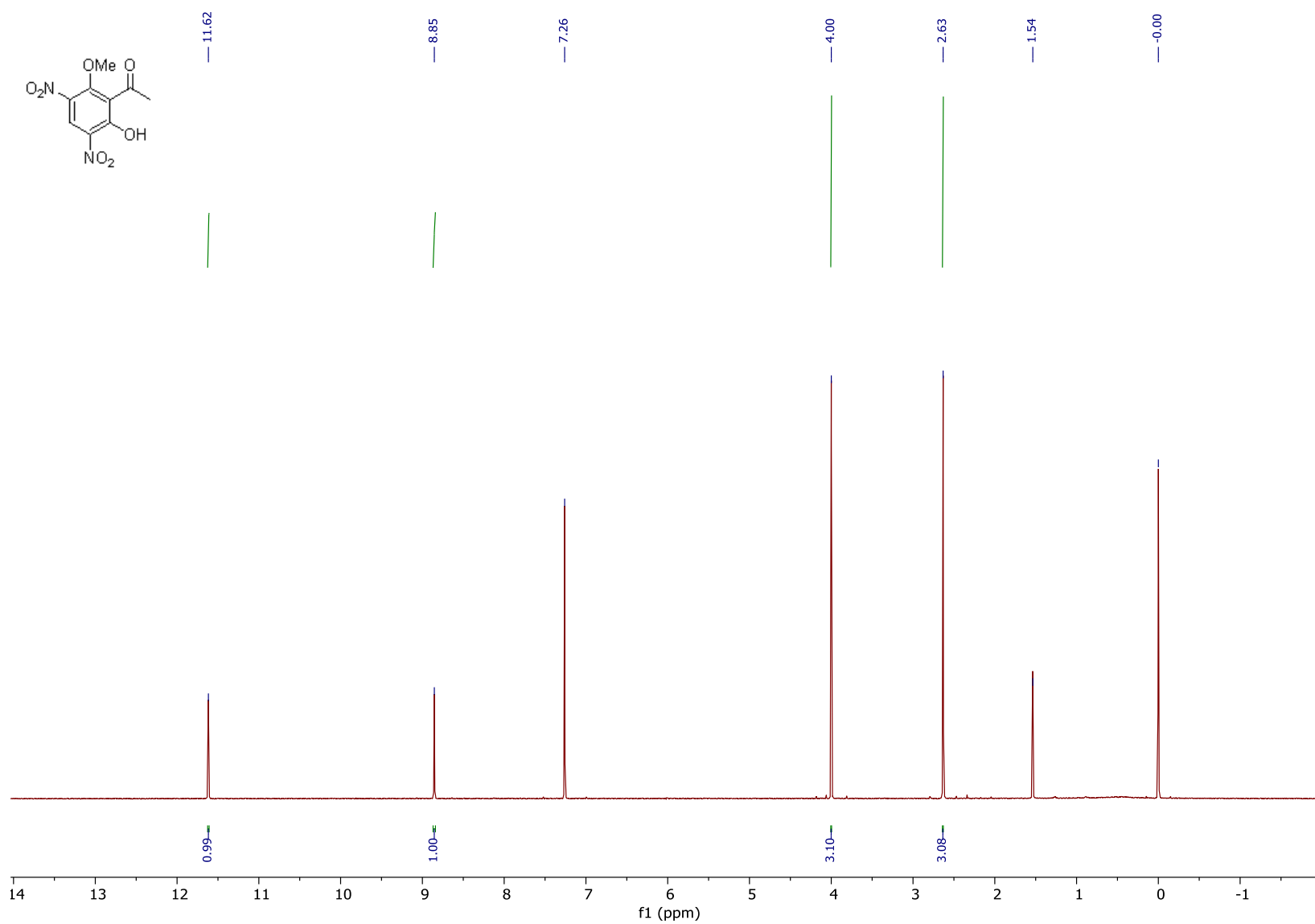


Figure 39: ¹H NMR of Compound **137**

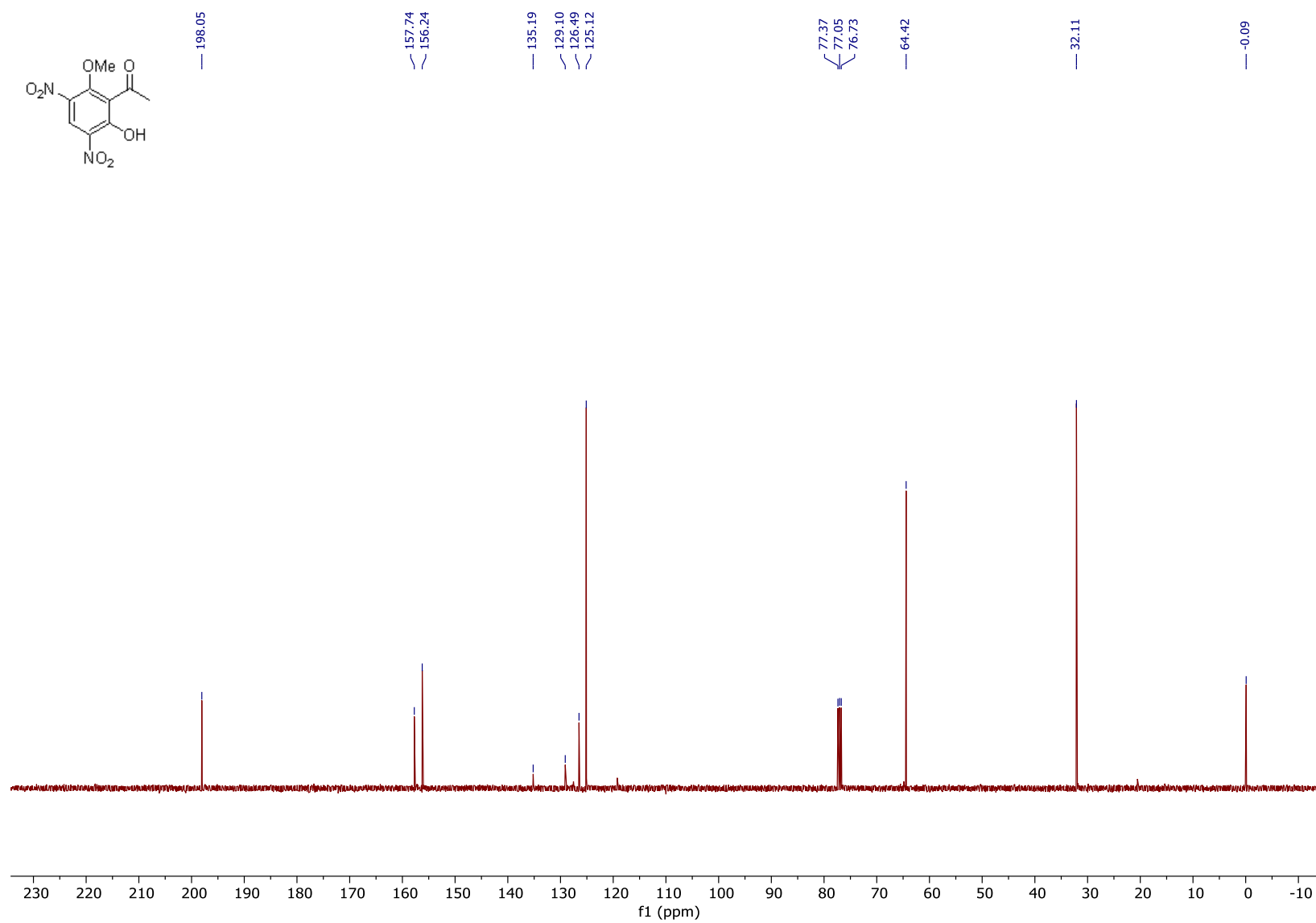


Figure 40: ^{13}C NMR of Compound **137**

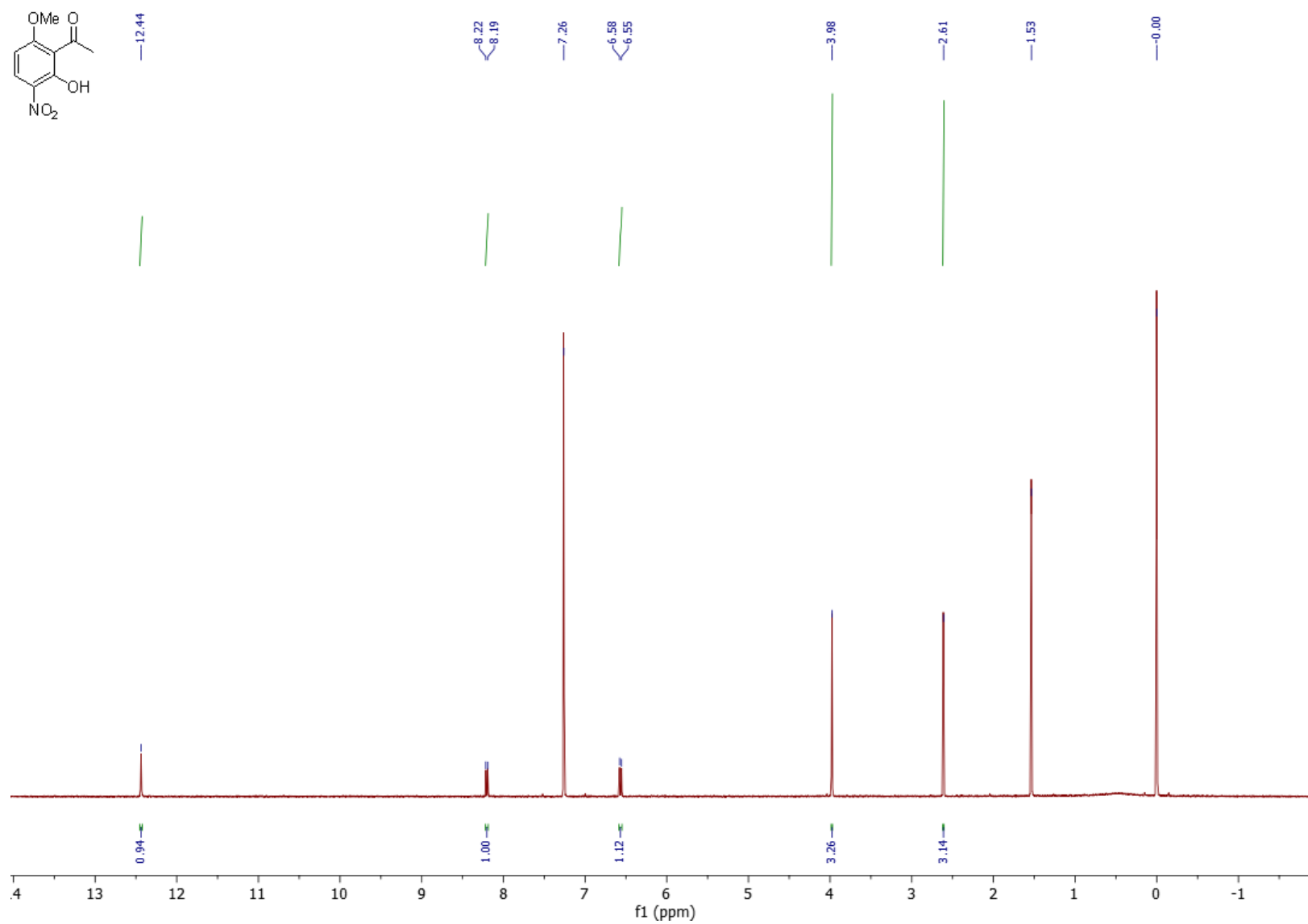


Figure 41: ¹H NMR of Compound **138**

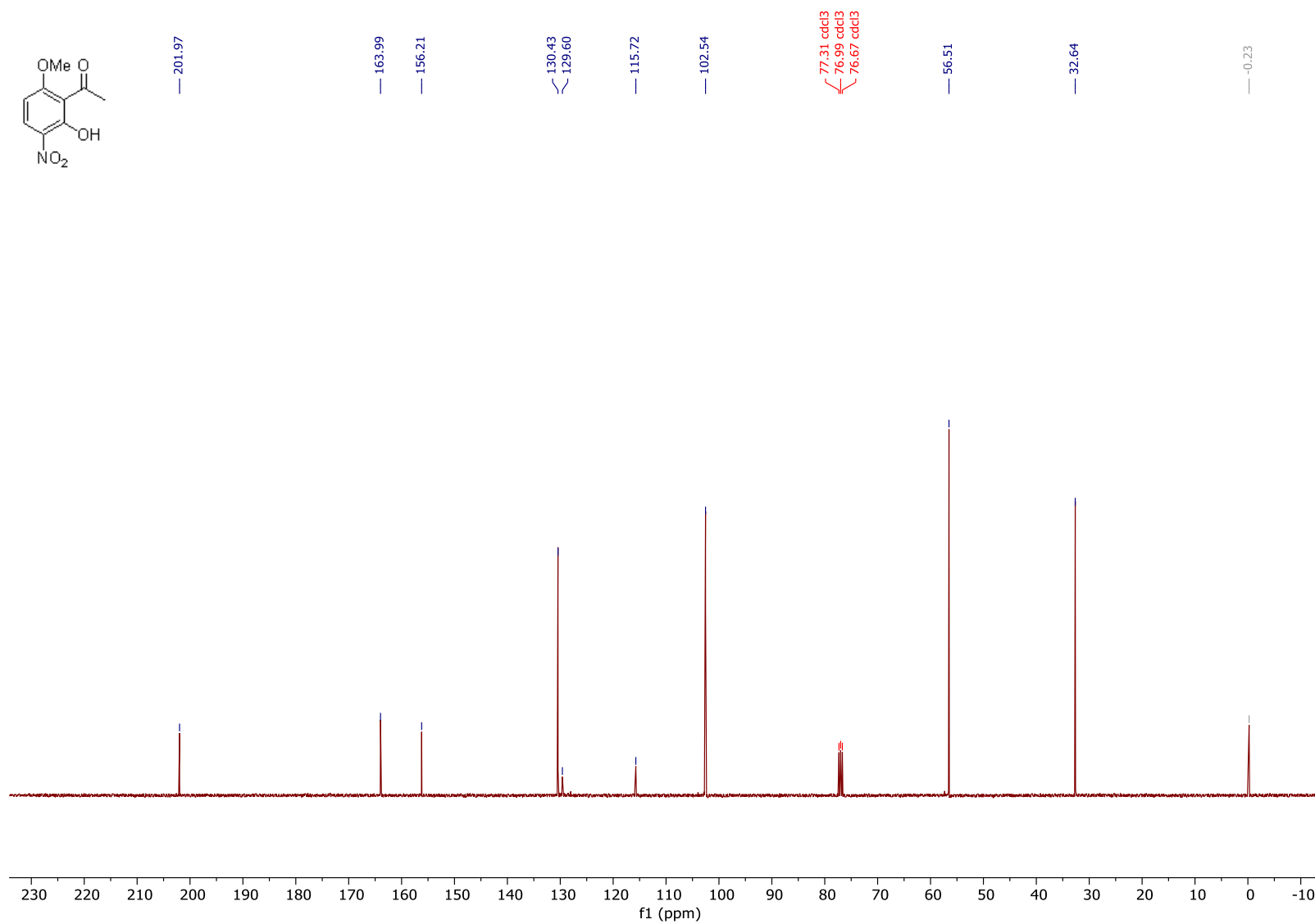


Figure 42: ^{13}C NMR of Compound **138**

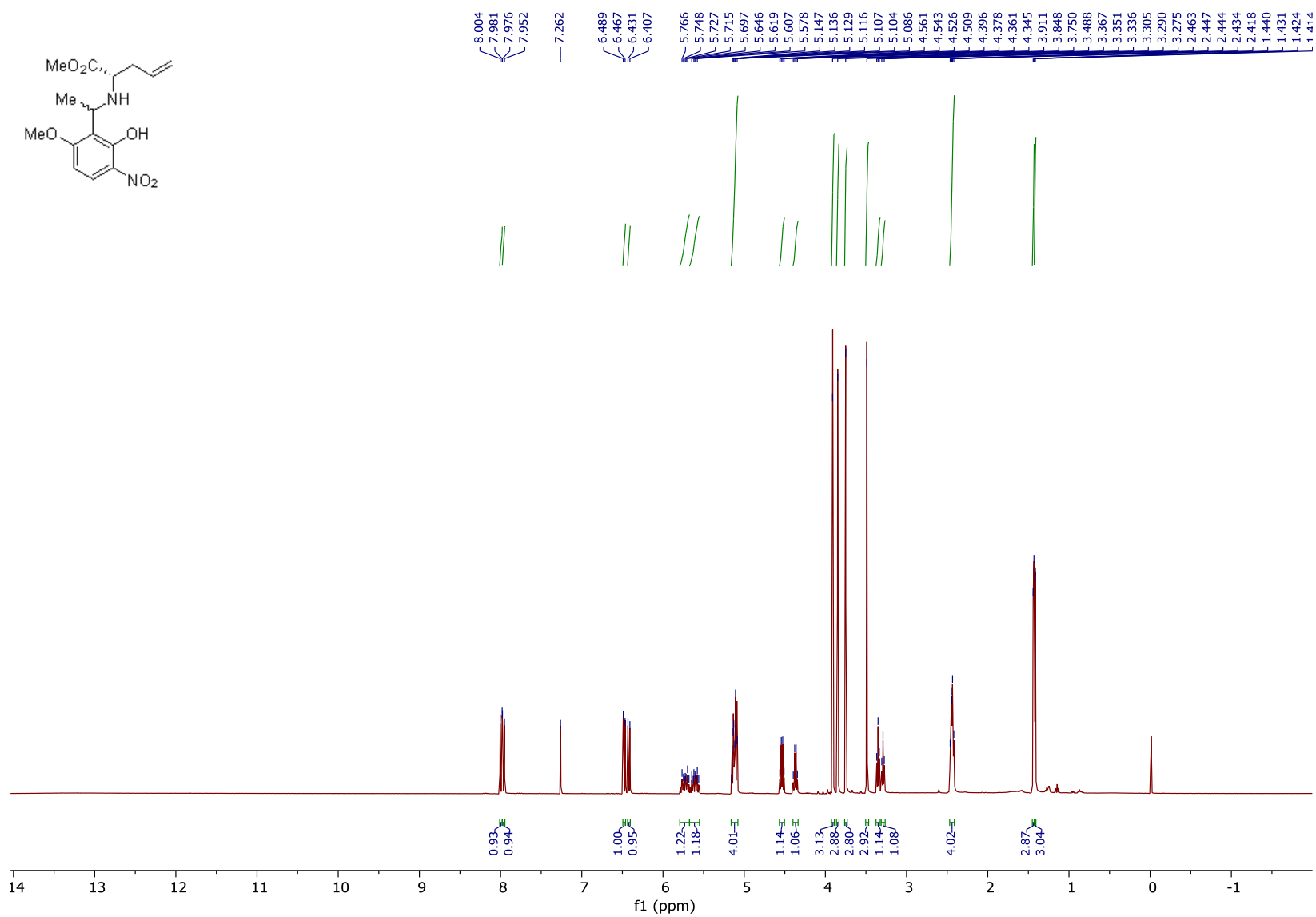


Figure 43: ¹H NMR of Compound **140** racemic mixture

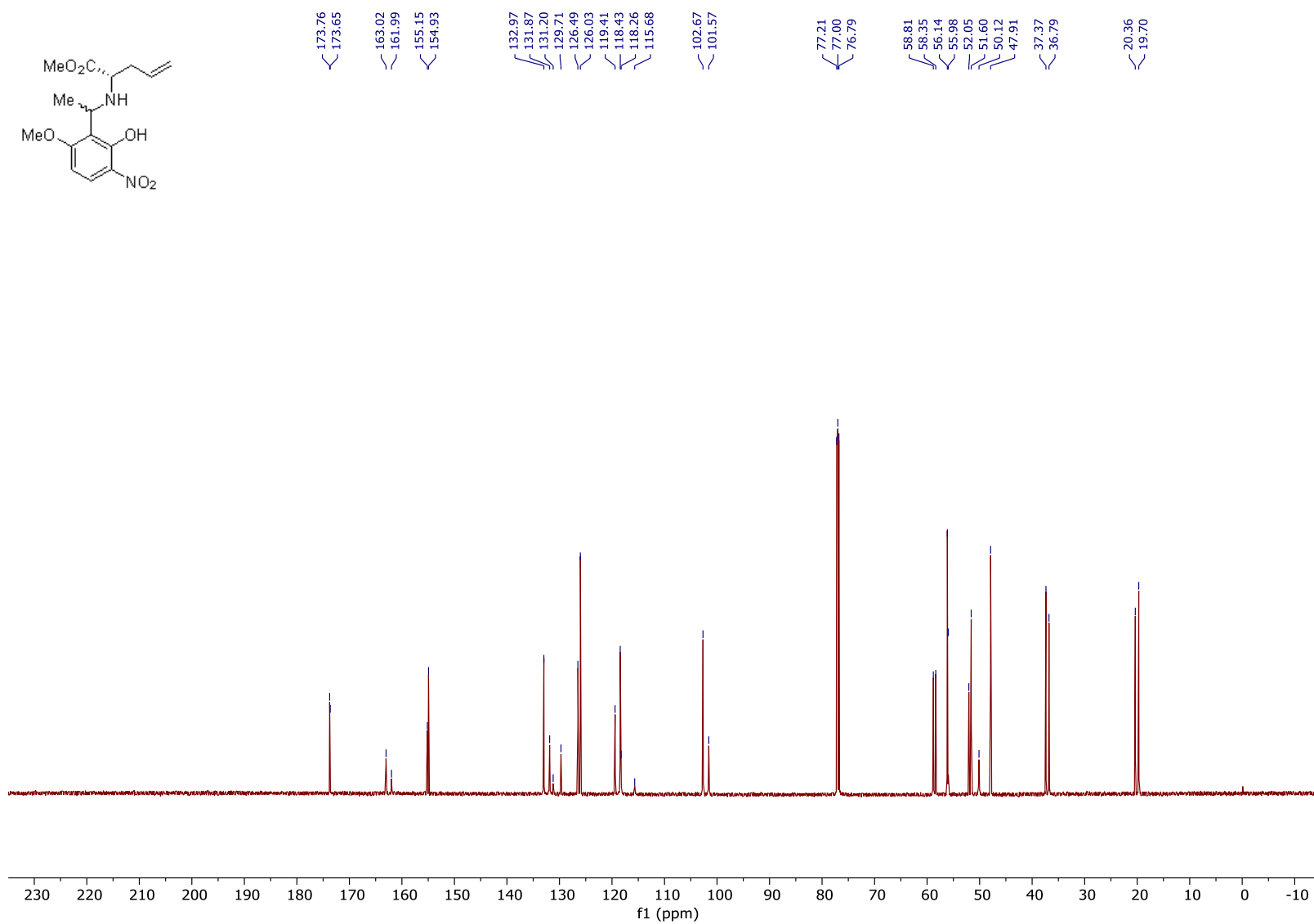


Figure 44: ¹³C NMR of Compound **140** racemic mixture

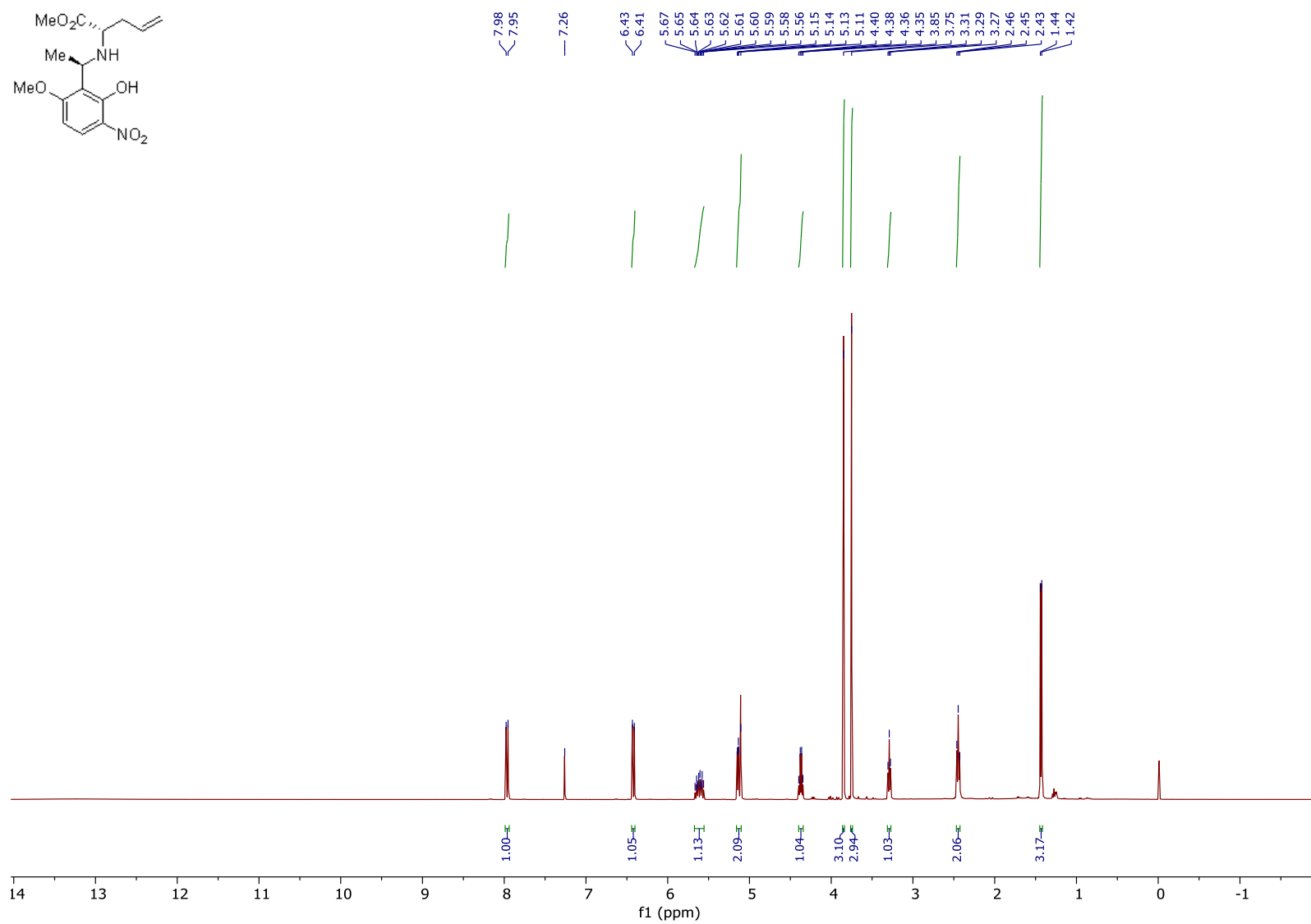


Figure 45: ¹H NMR of Compound **140** single isomer

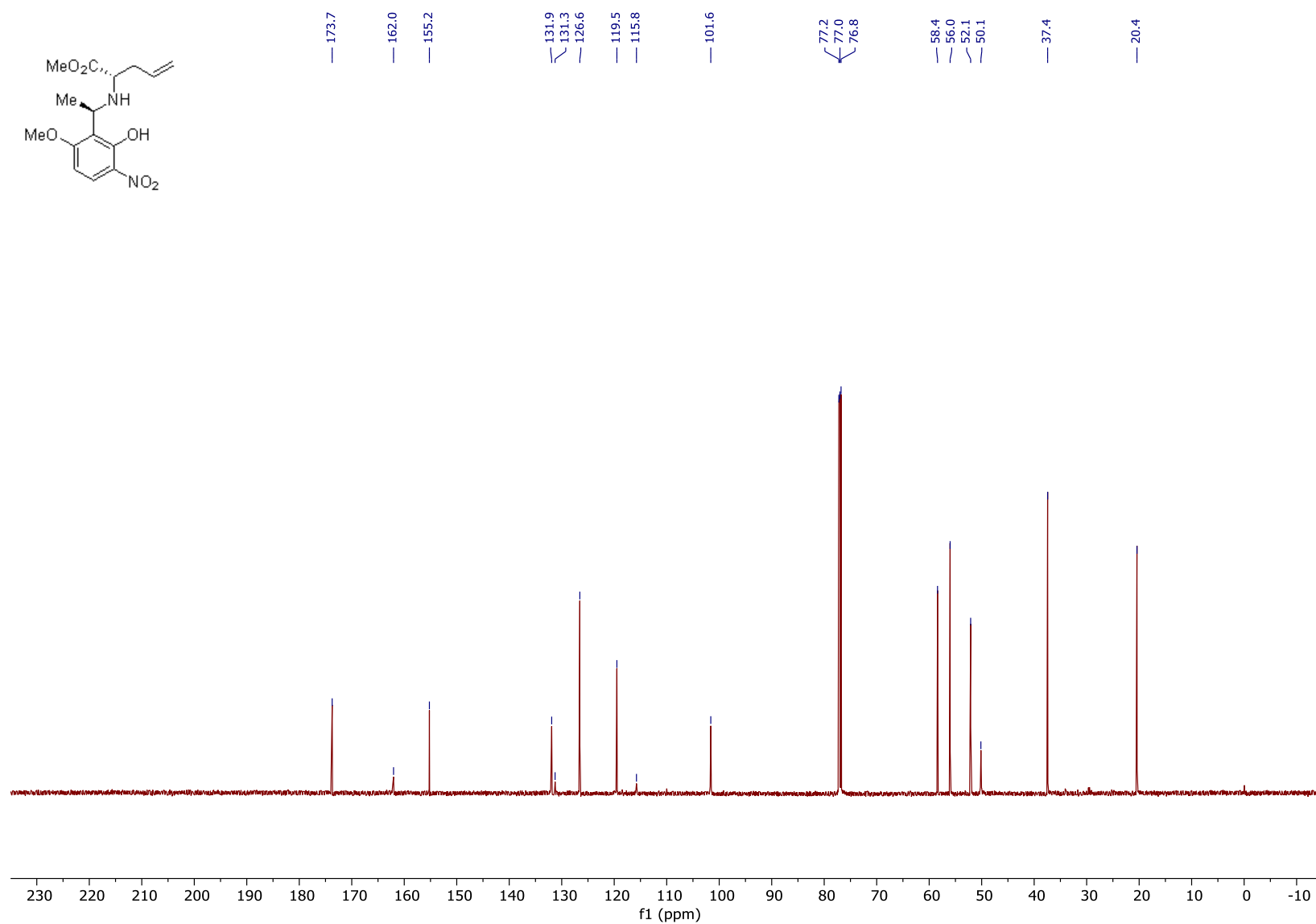


Figure 46: ¹³C NMR of Compound **140** single isomer

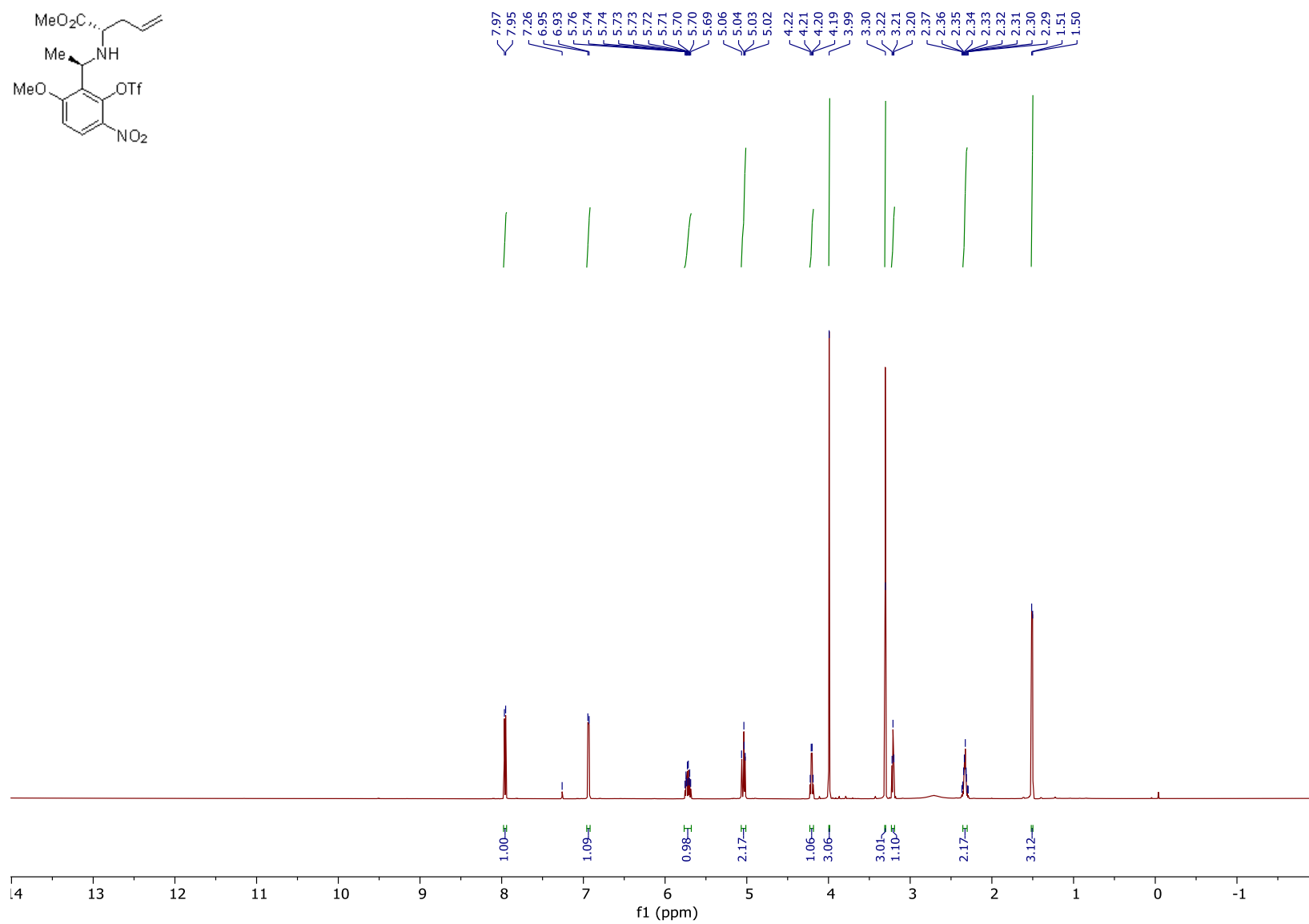


Figure 47: ^1H NMR of Compound **142**

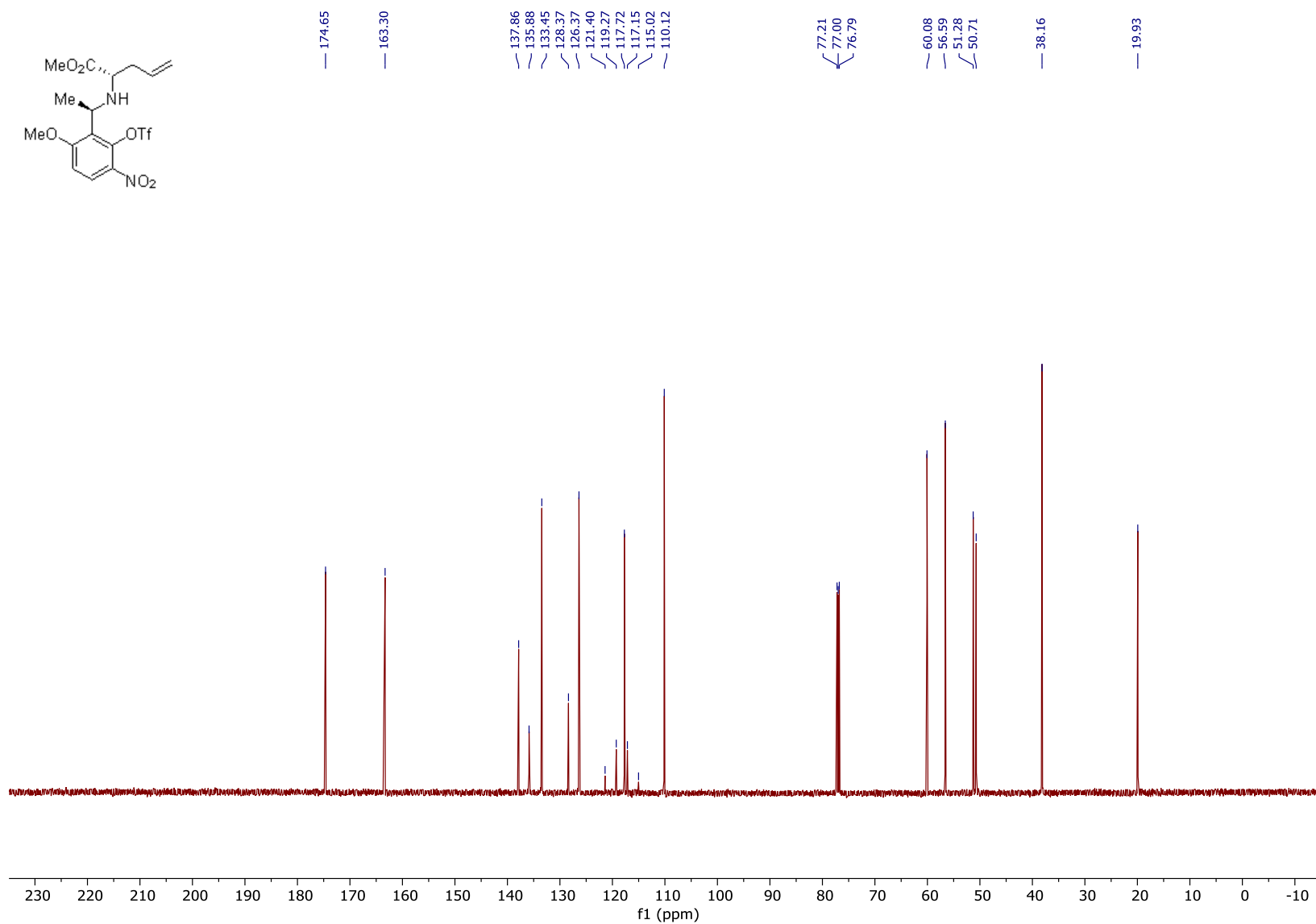


Figure 48: ^{13}C NMR of Compound **142**

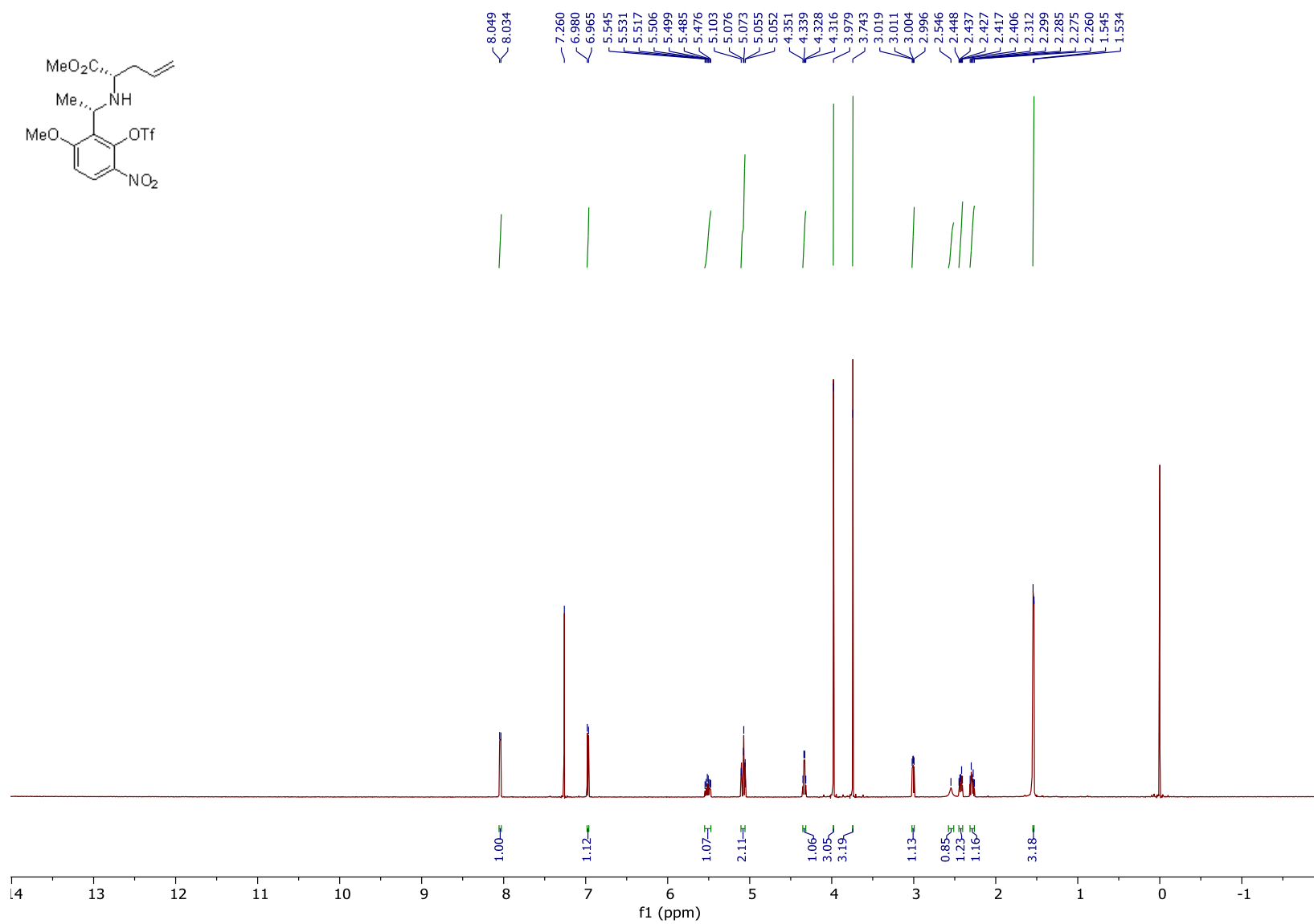


Figure 49: ^1H NMR of Compound **143**

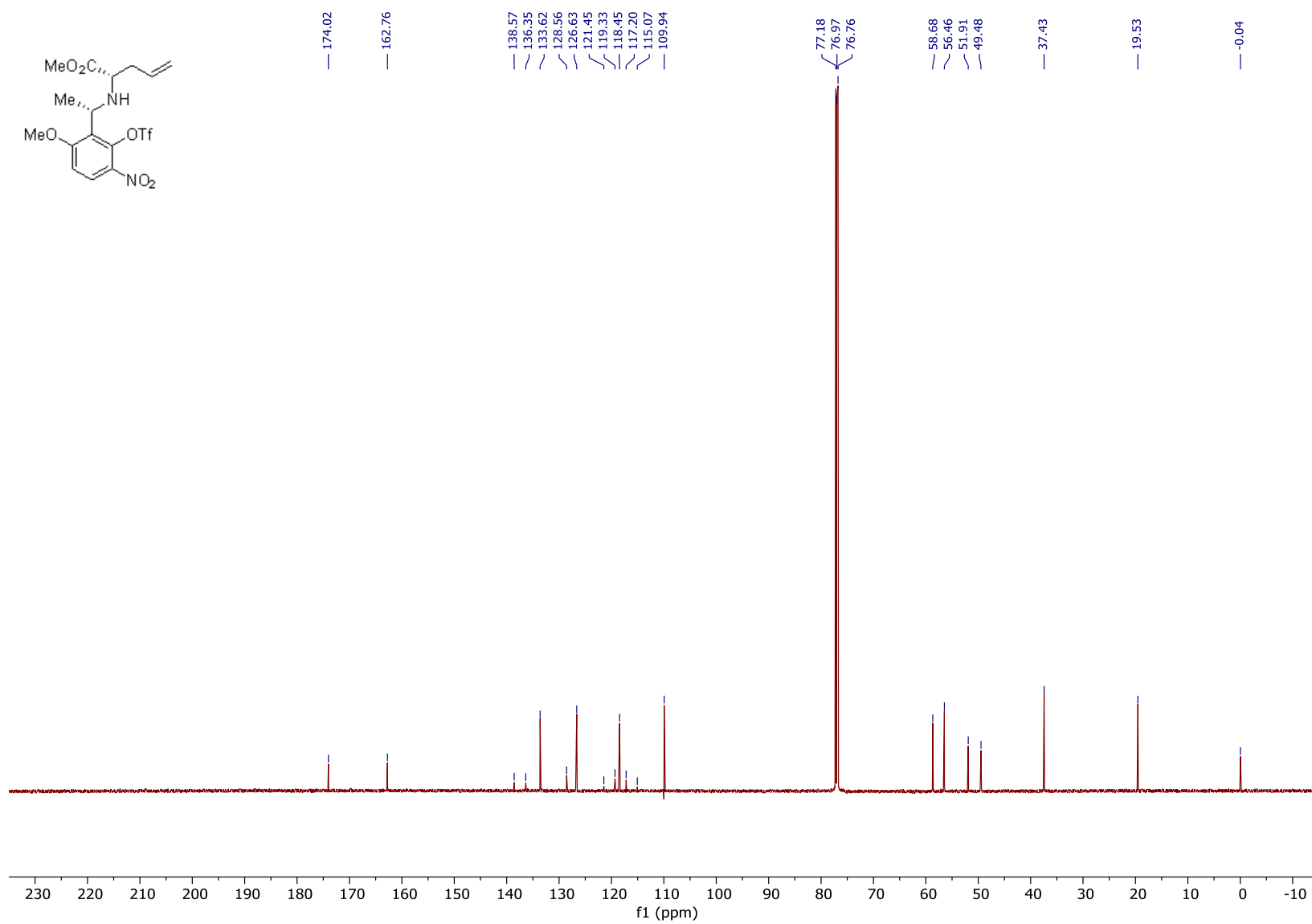


Figure 50: ¹³C NMR of Compound **143**

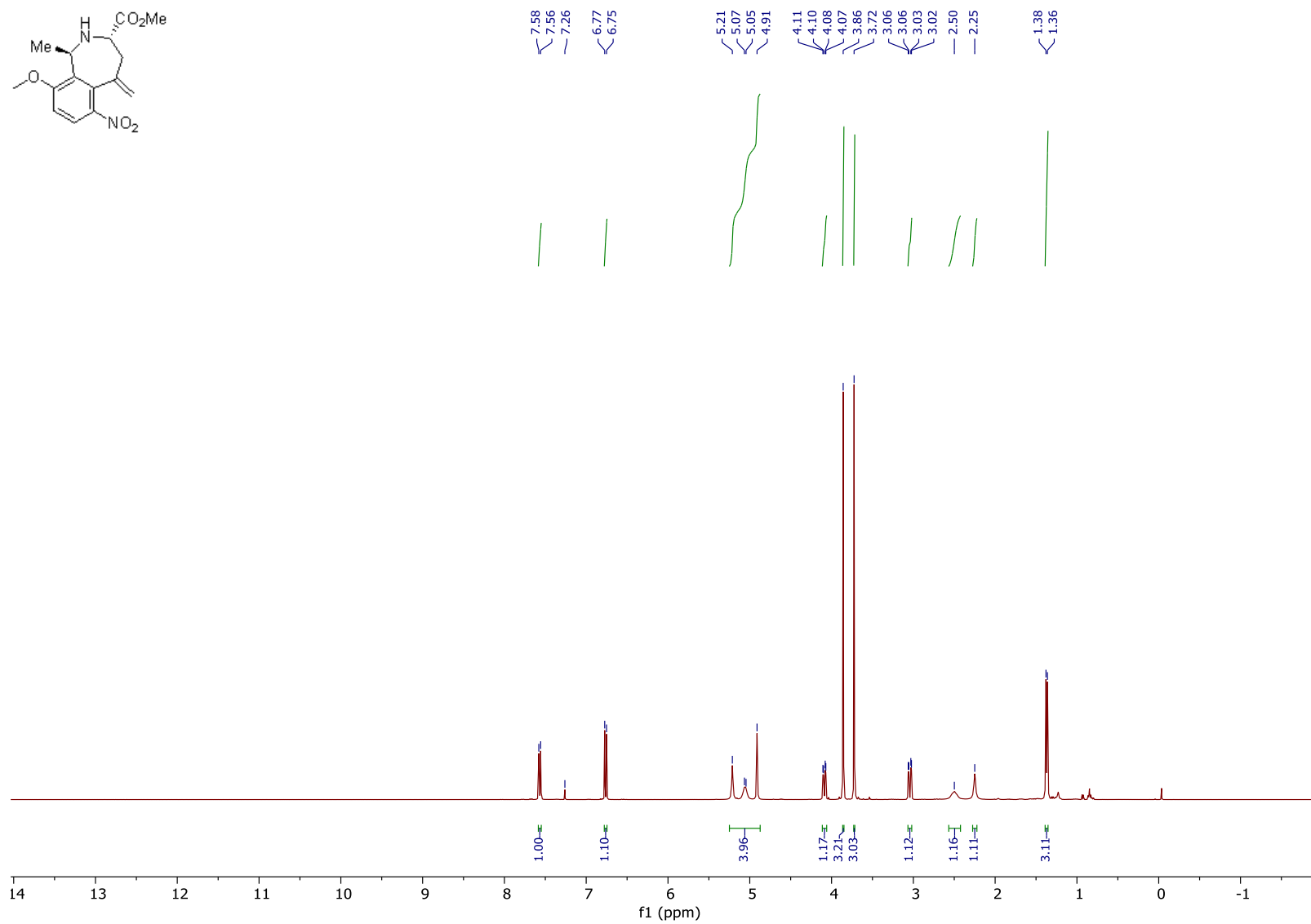


Figure 51: ¹H NMR of Compound **144**

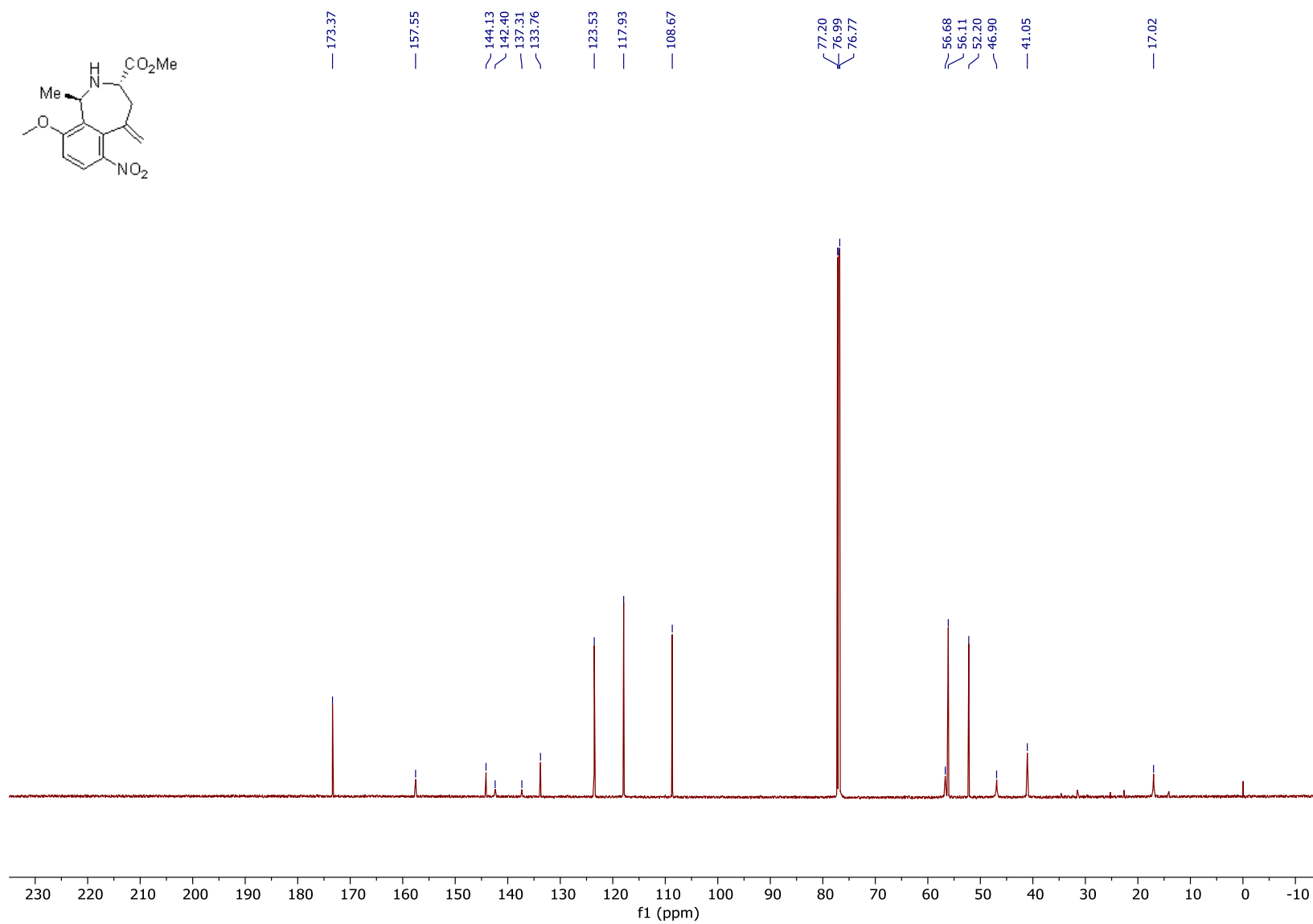


Figure 52: ^{13}C NMR of Compound **144**

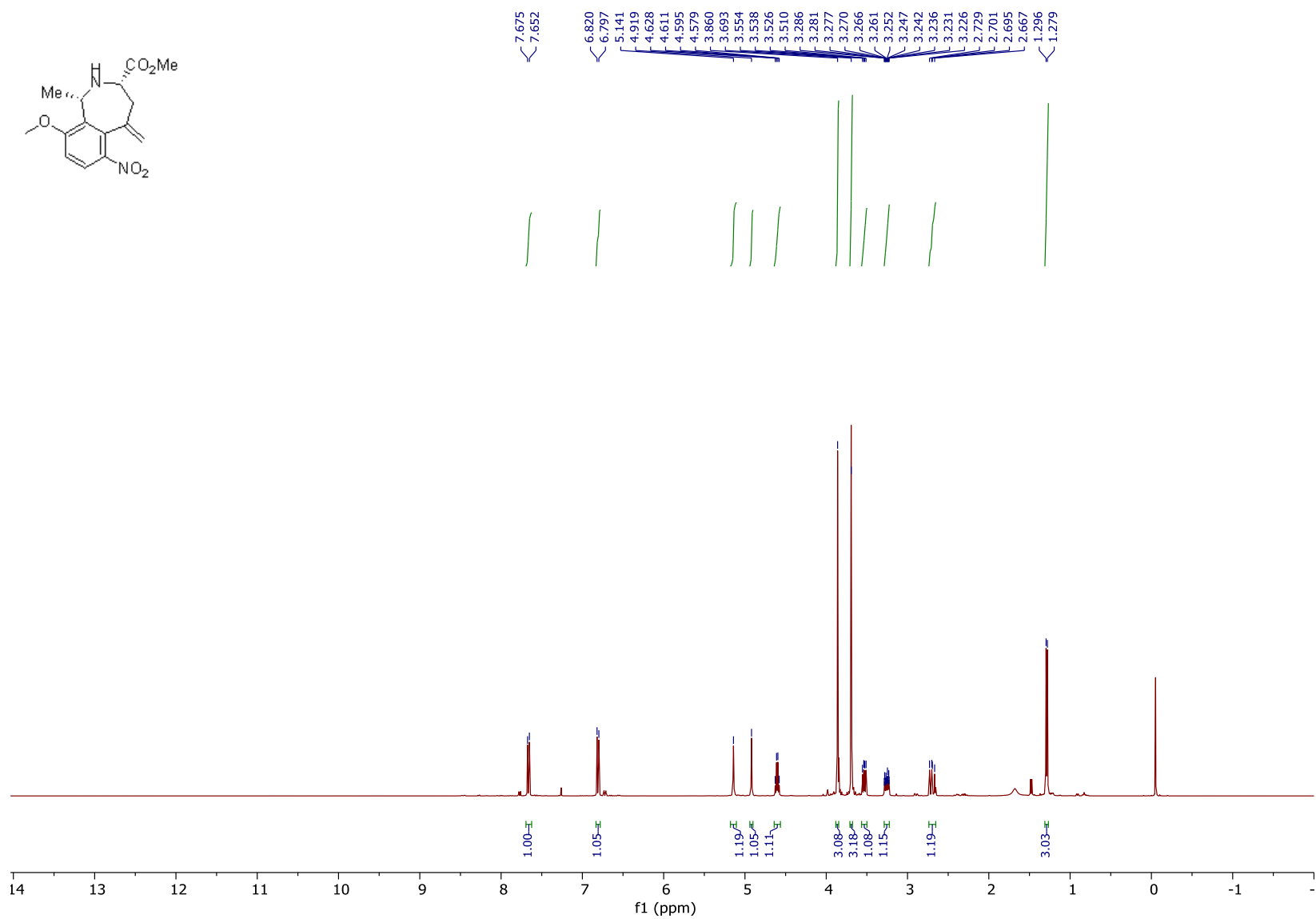


Figure 53: ¹H NMR of Compound 145

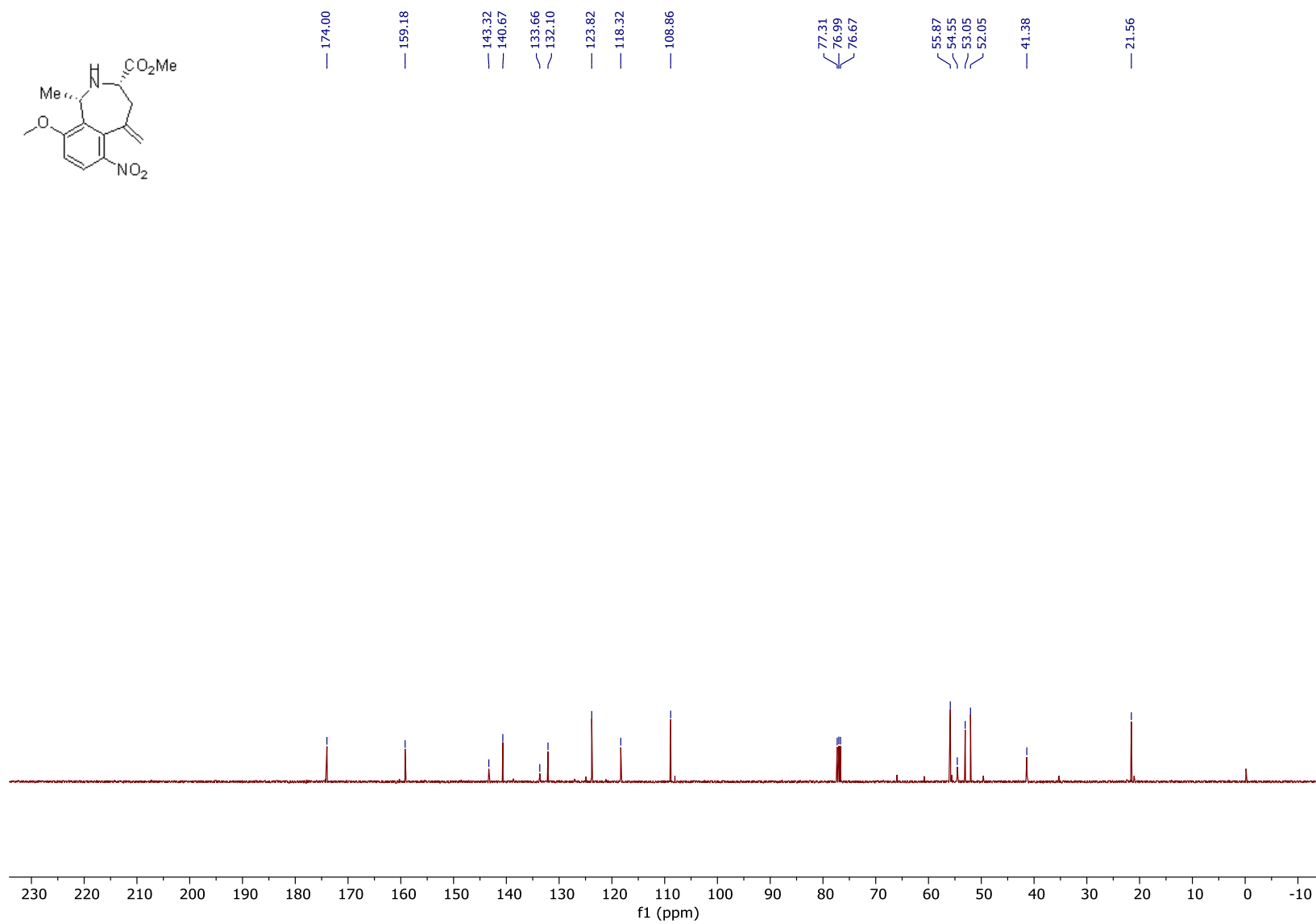


Figure 54: ¹³C NMR of Compound **145**

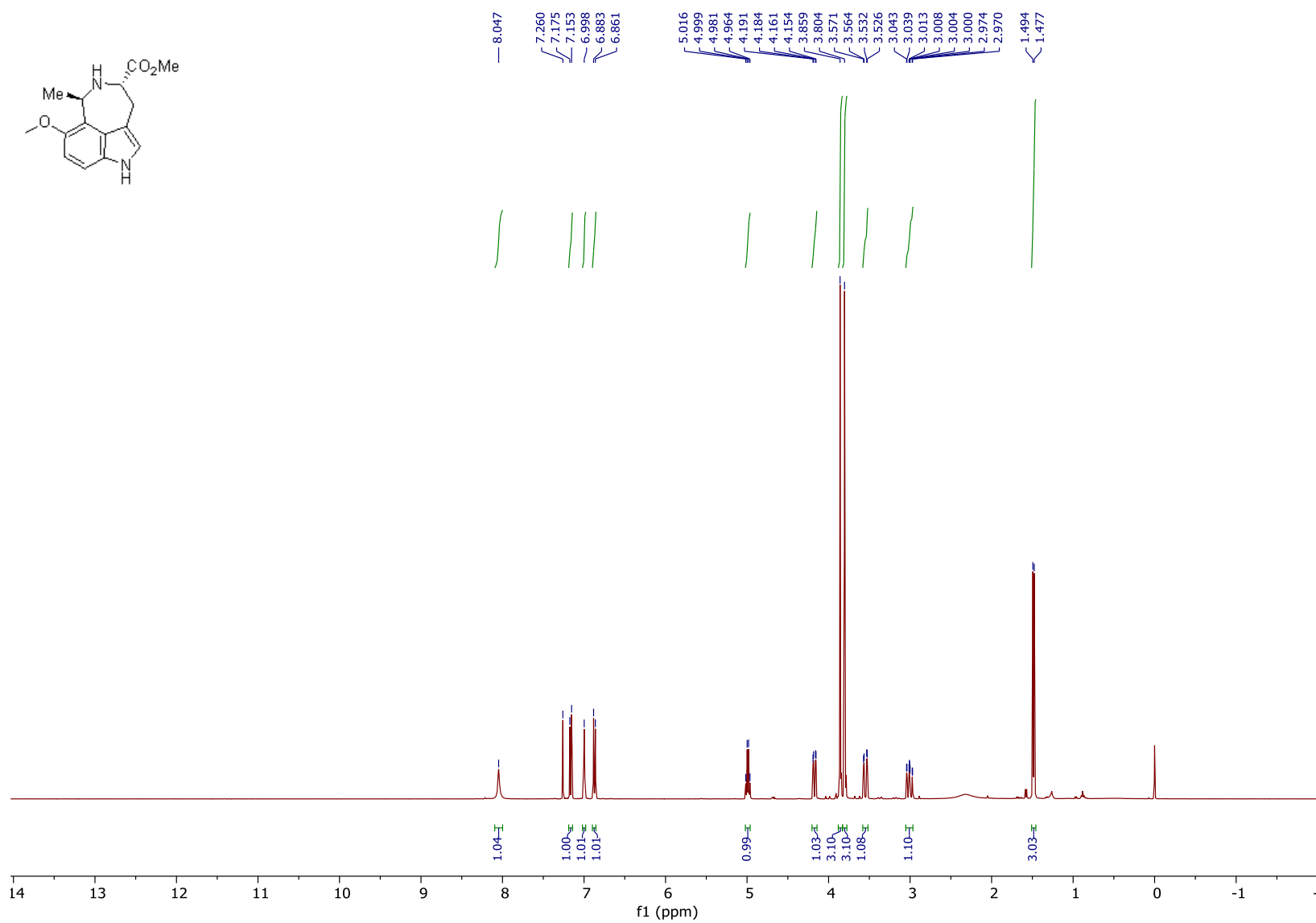


Figure 55: ^1H NMR of Compound **146**

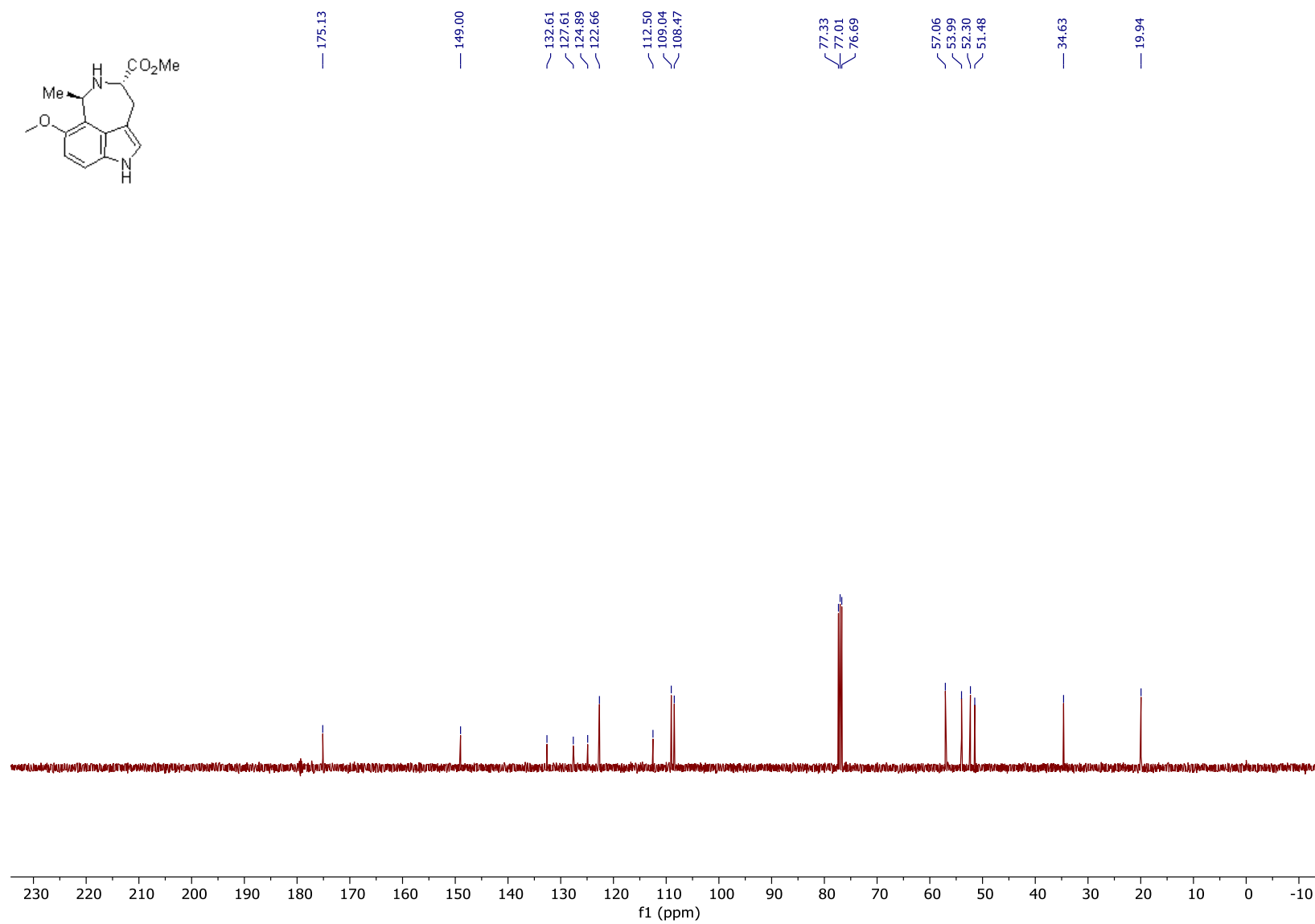


Figure 56: ^{13}C NMR of Compound **146**

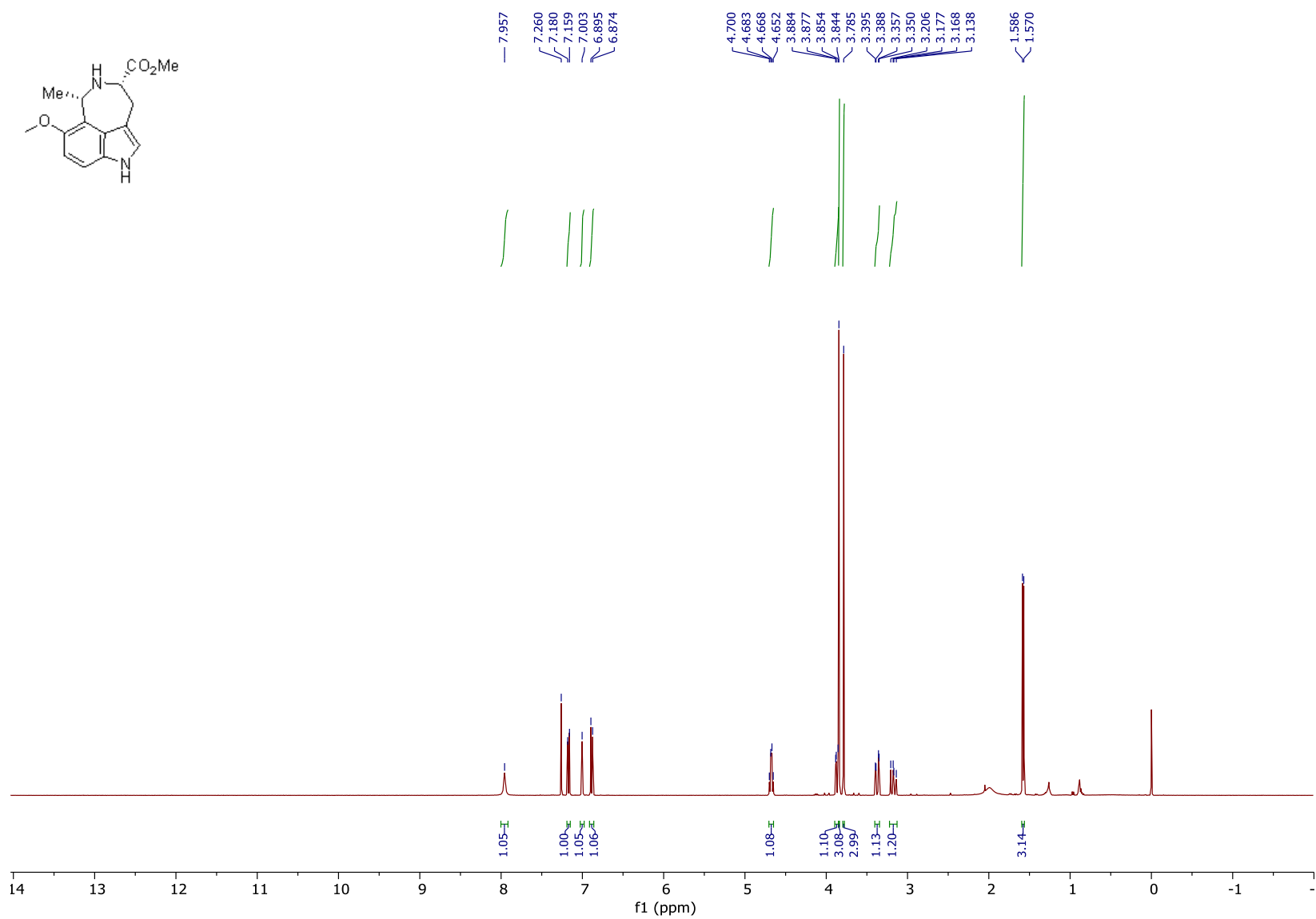


Figure 57: ¹H NMR of Compound **147**

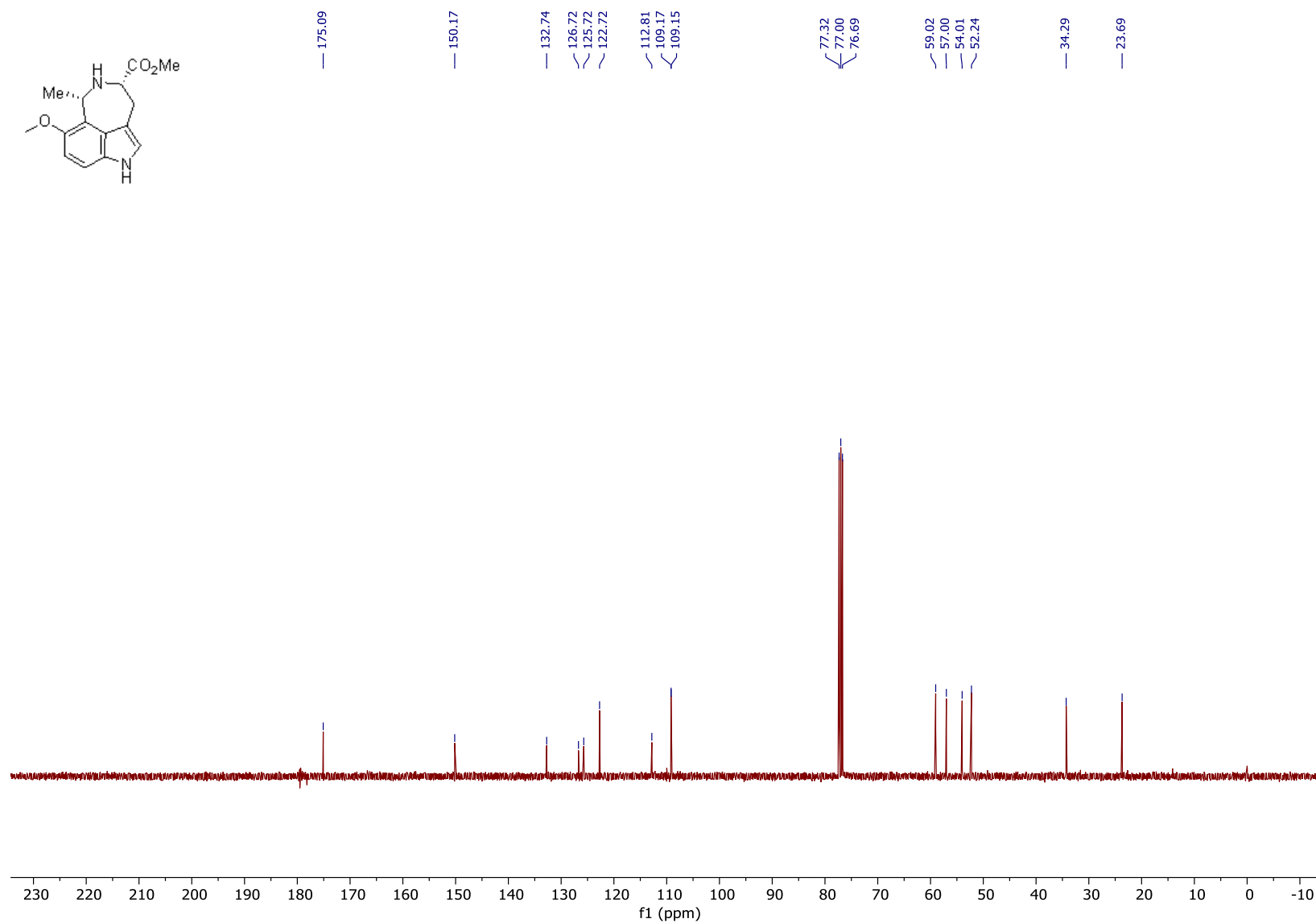


Figure 58: ^{13}C NMR of Compound 147

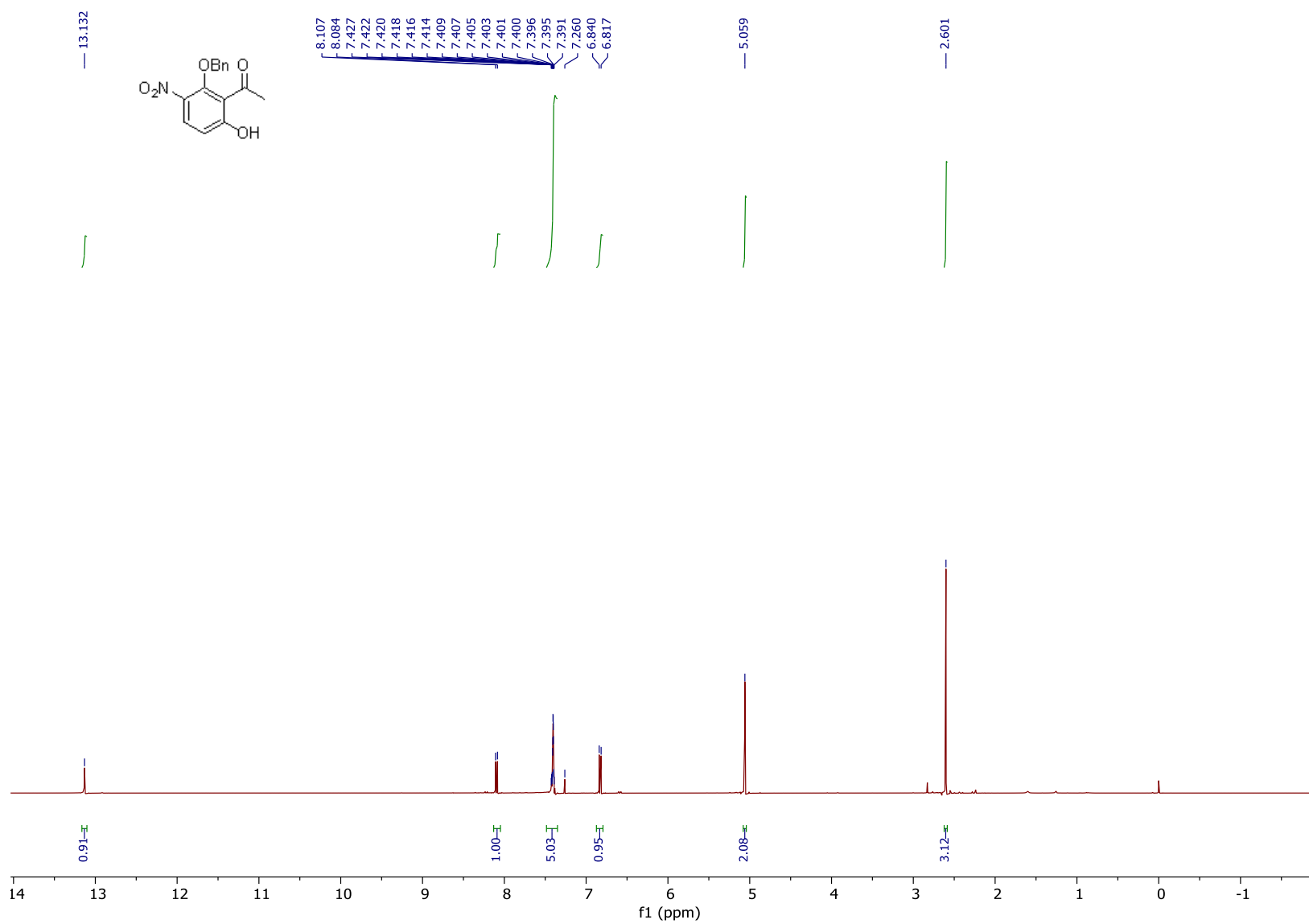


Figure 59: ¹H NMR of Compound **149**

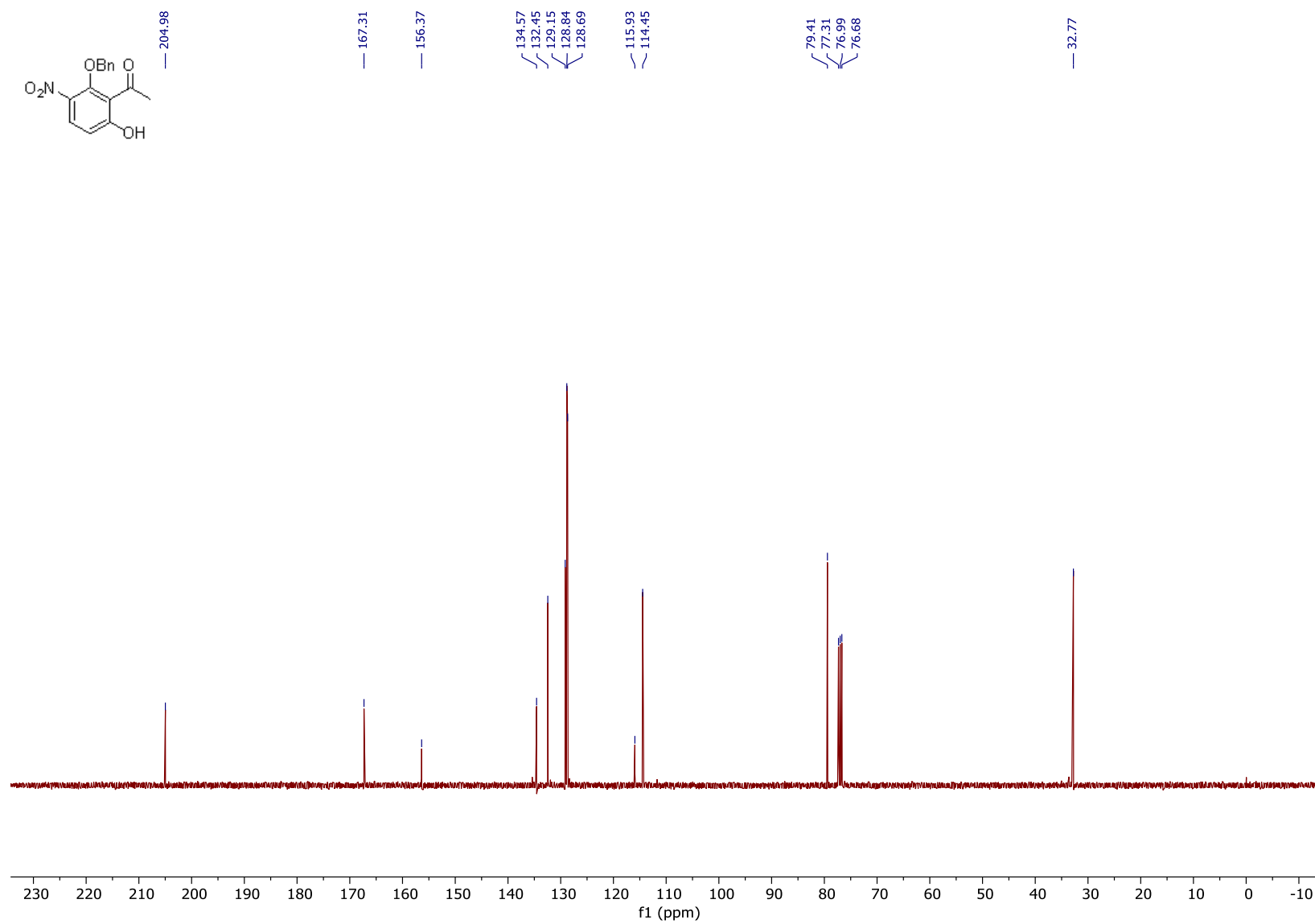


Figure 60: ^{13}C NMR of Compound **149**

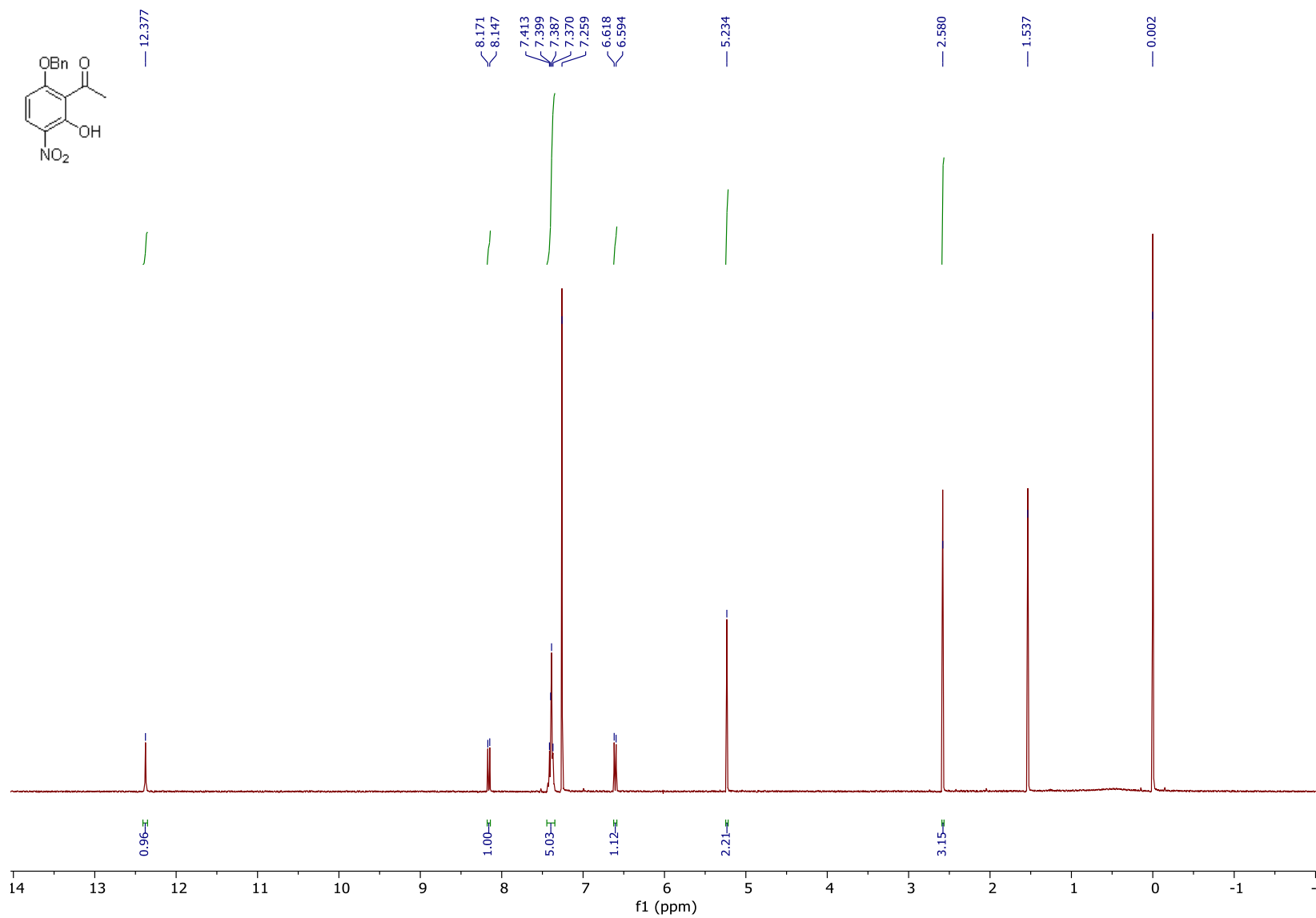


Figure 61: ¹H NMR of Compound **150**

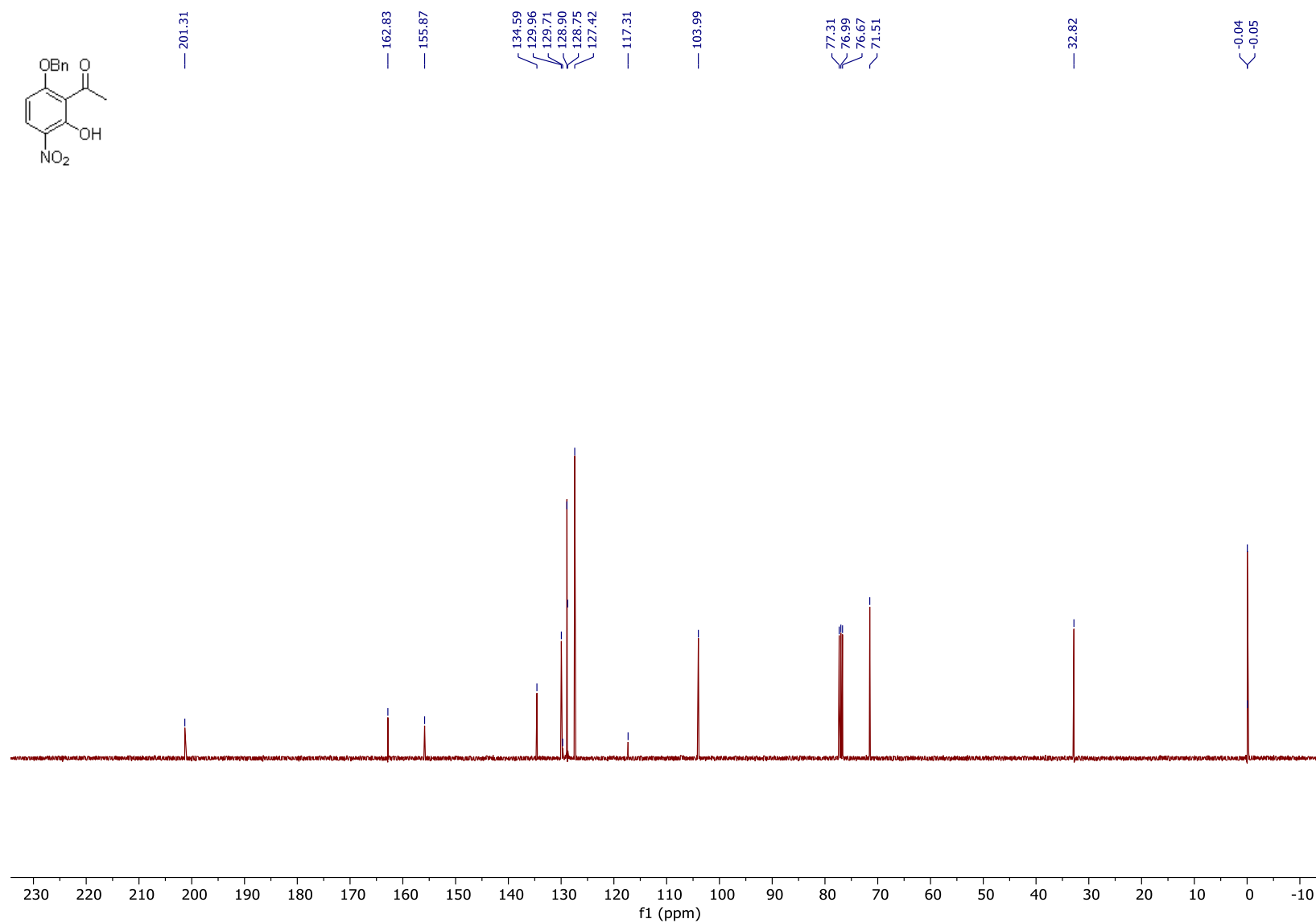


Figure 62: ¹³C NMR of Compound **150**

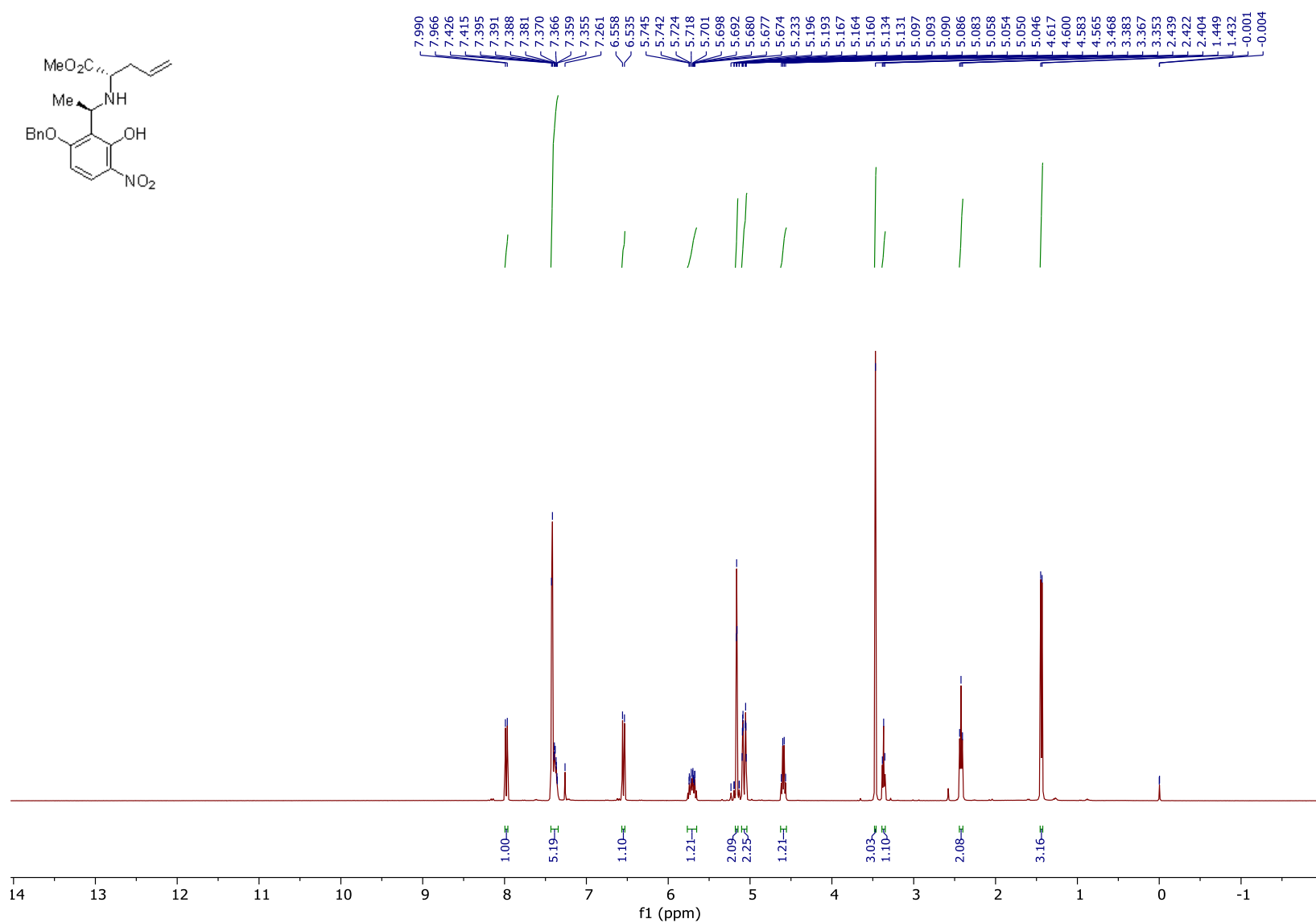


Figure 63: ¹H NMR of Compound **152**

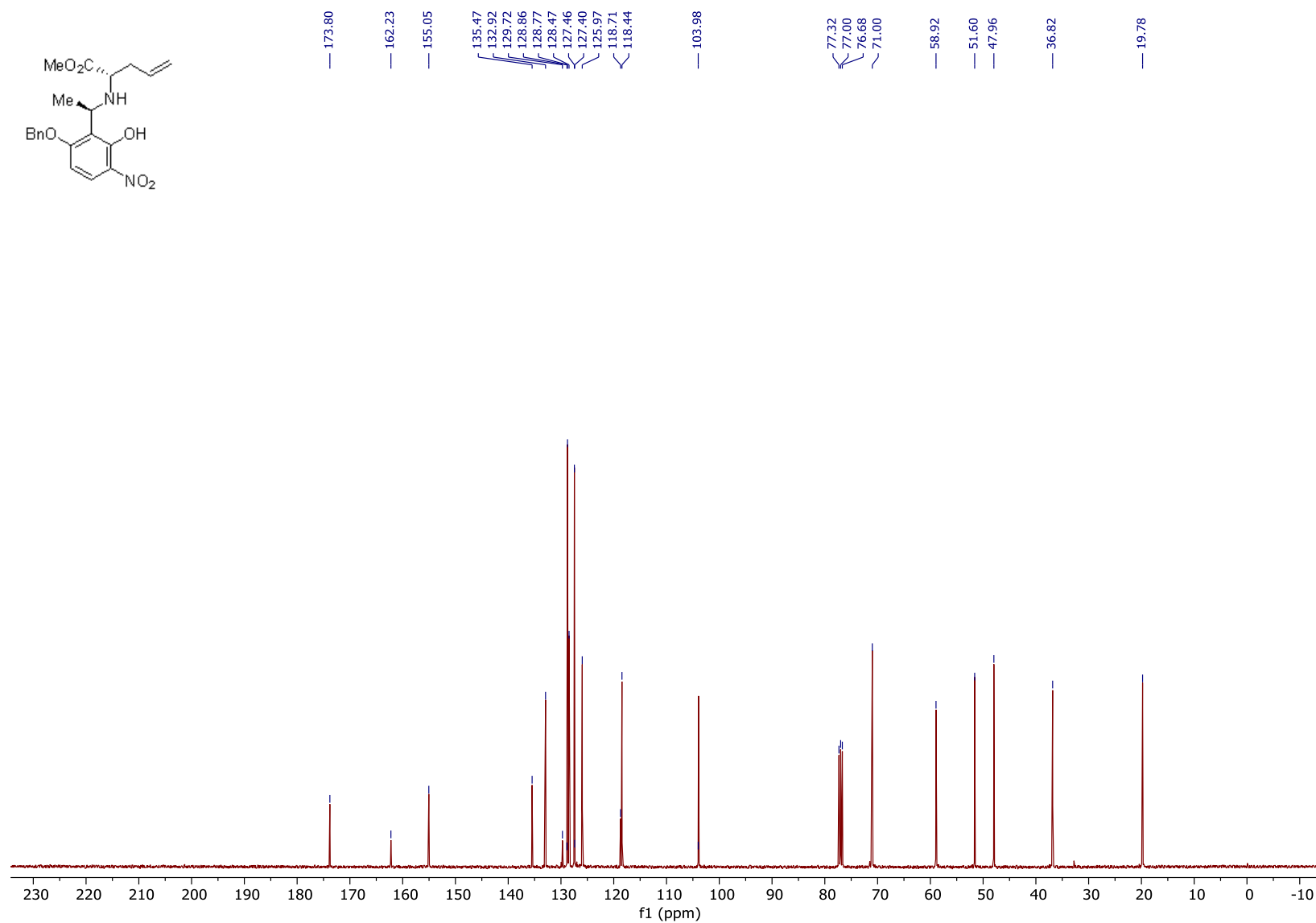


Figure 64: ^{13}C NMR of Compound **152**

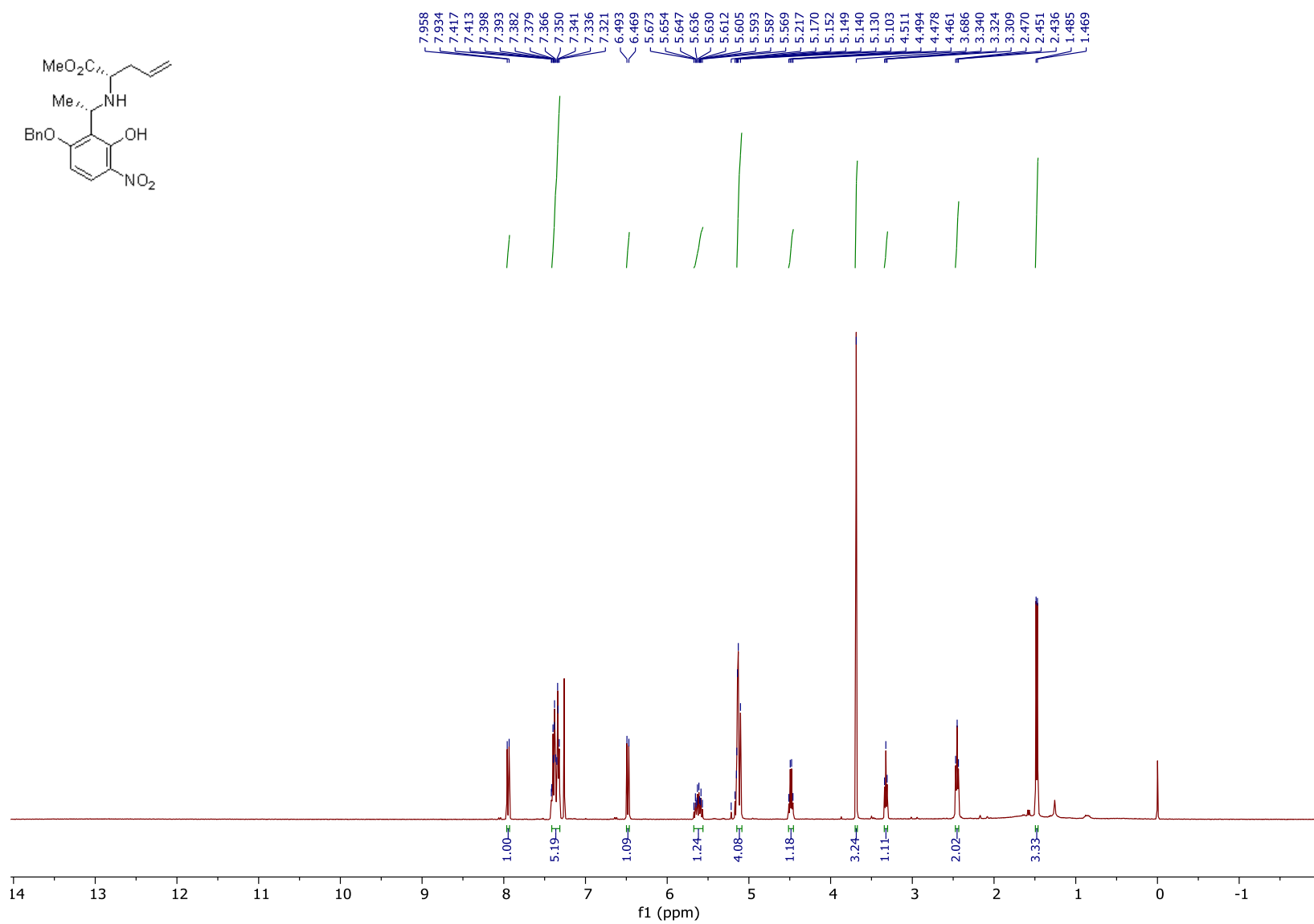


Figure 65: ¹H NMR of Compound **153**

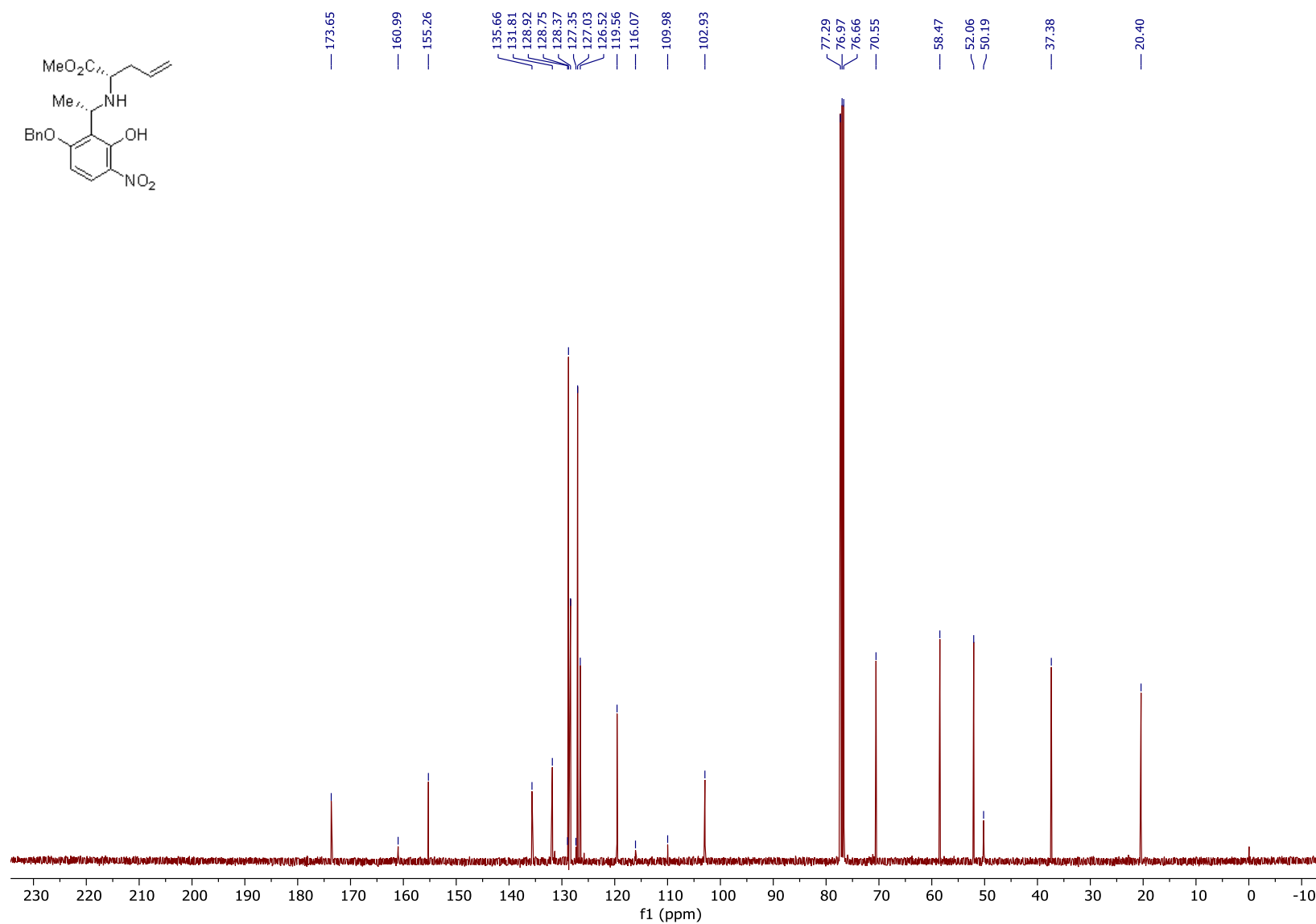


Figure 66: ^{13}C NMR of Compound **153**

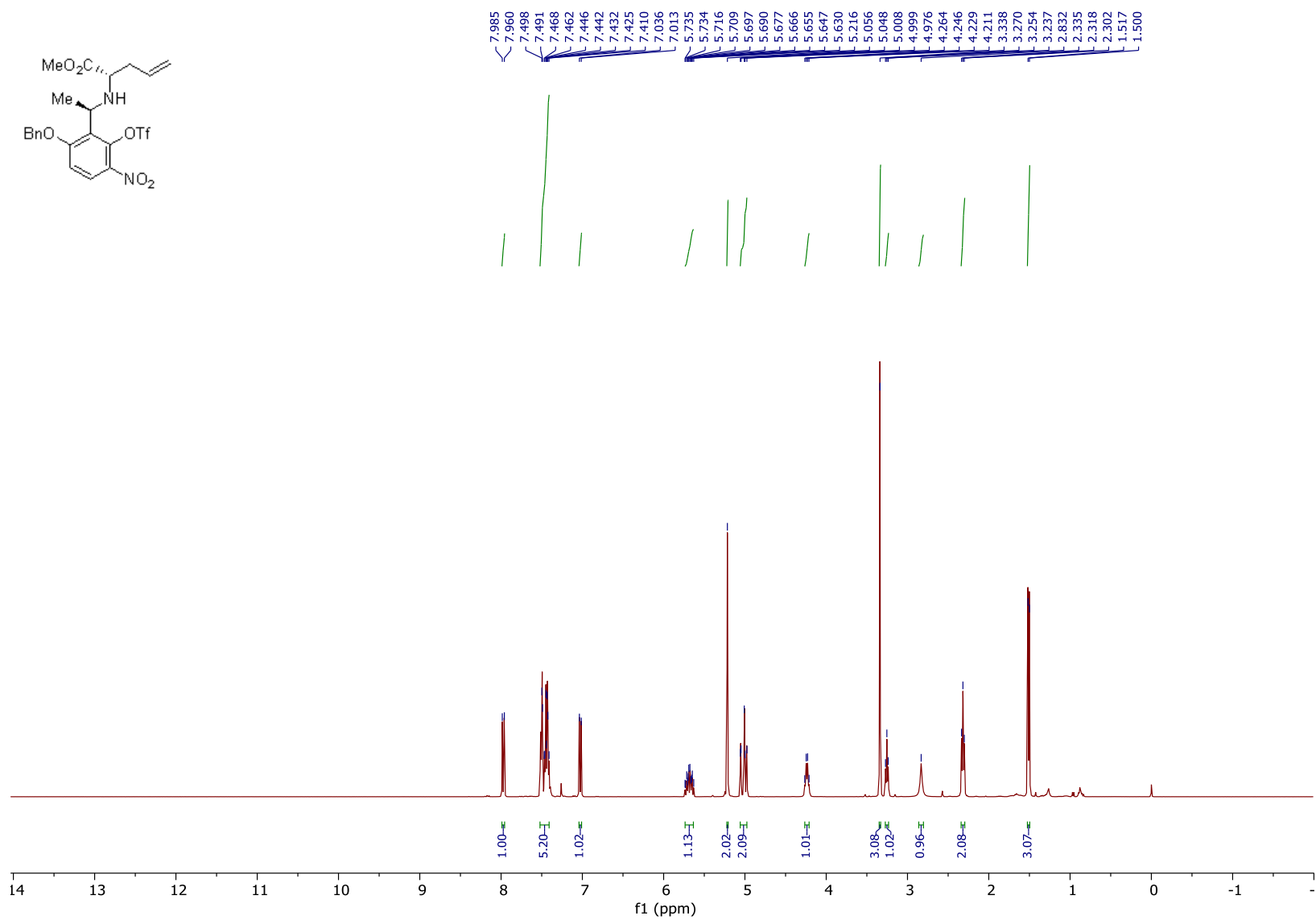


Figure 67: ¹H NMR of Compound **154**

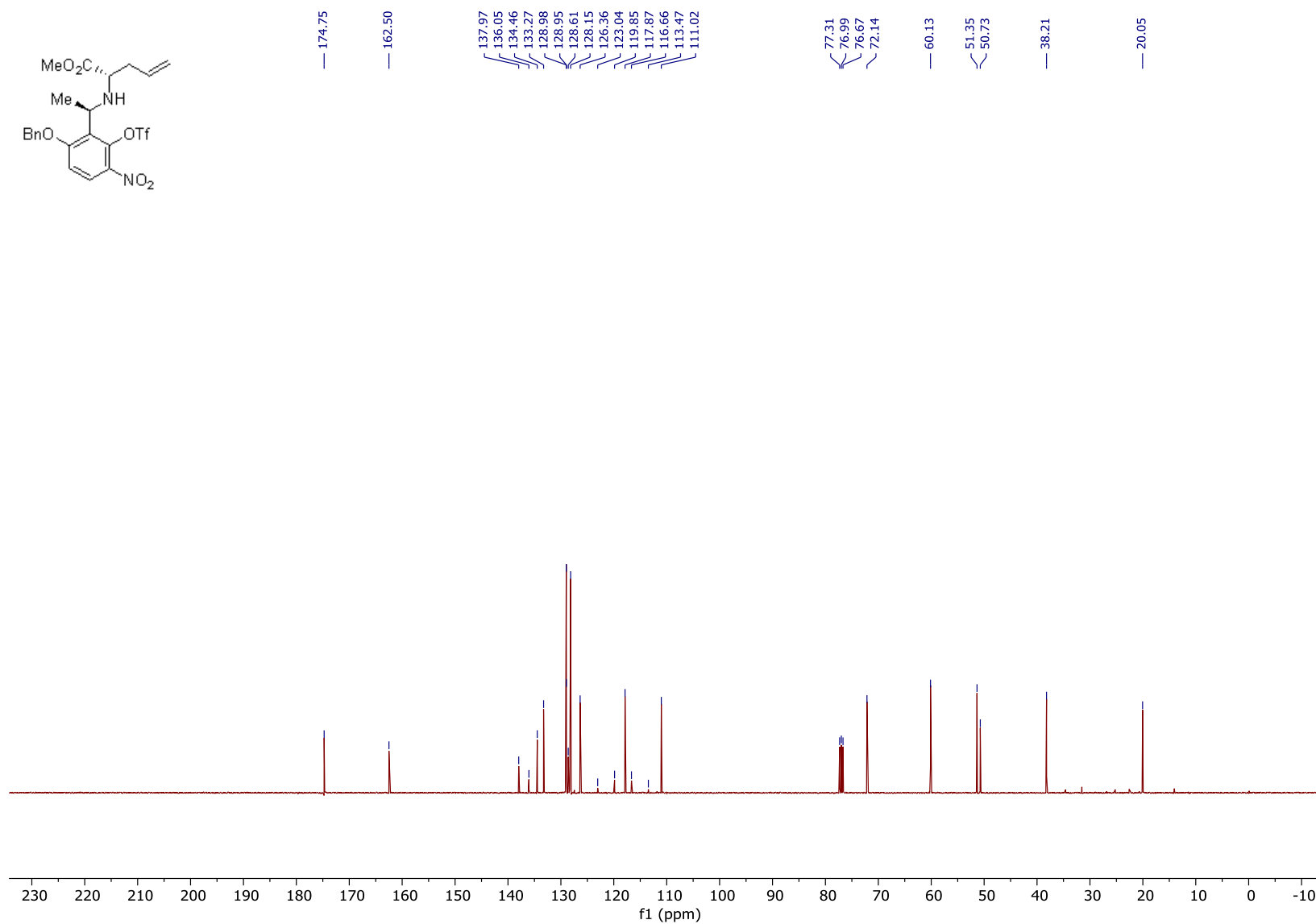


Figure 68: ^{13}C NMR of Compound **154**

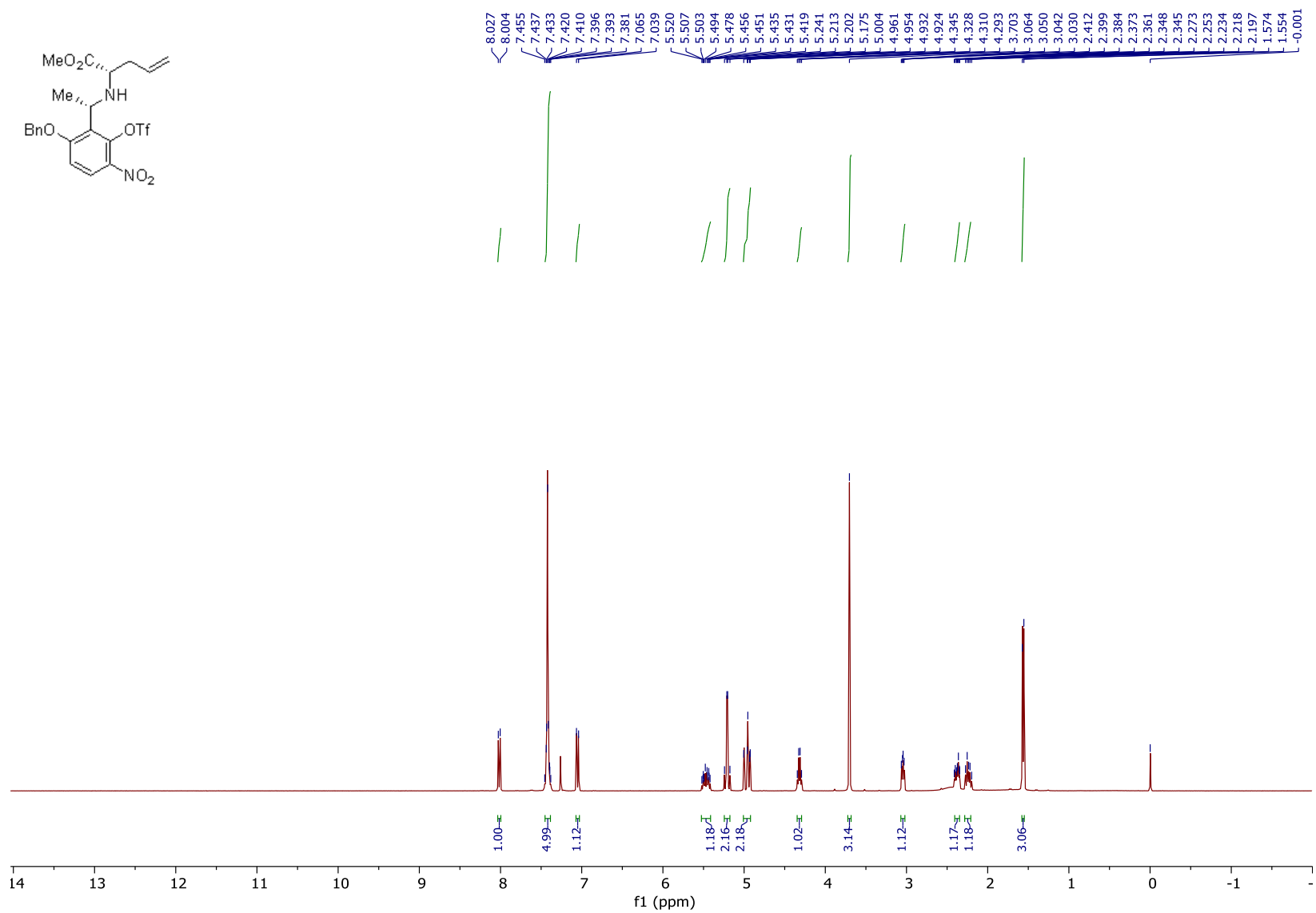


Figure 69: ¹H NMR of Compound 155

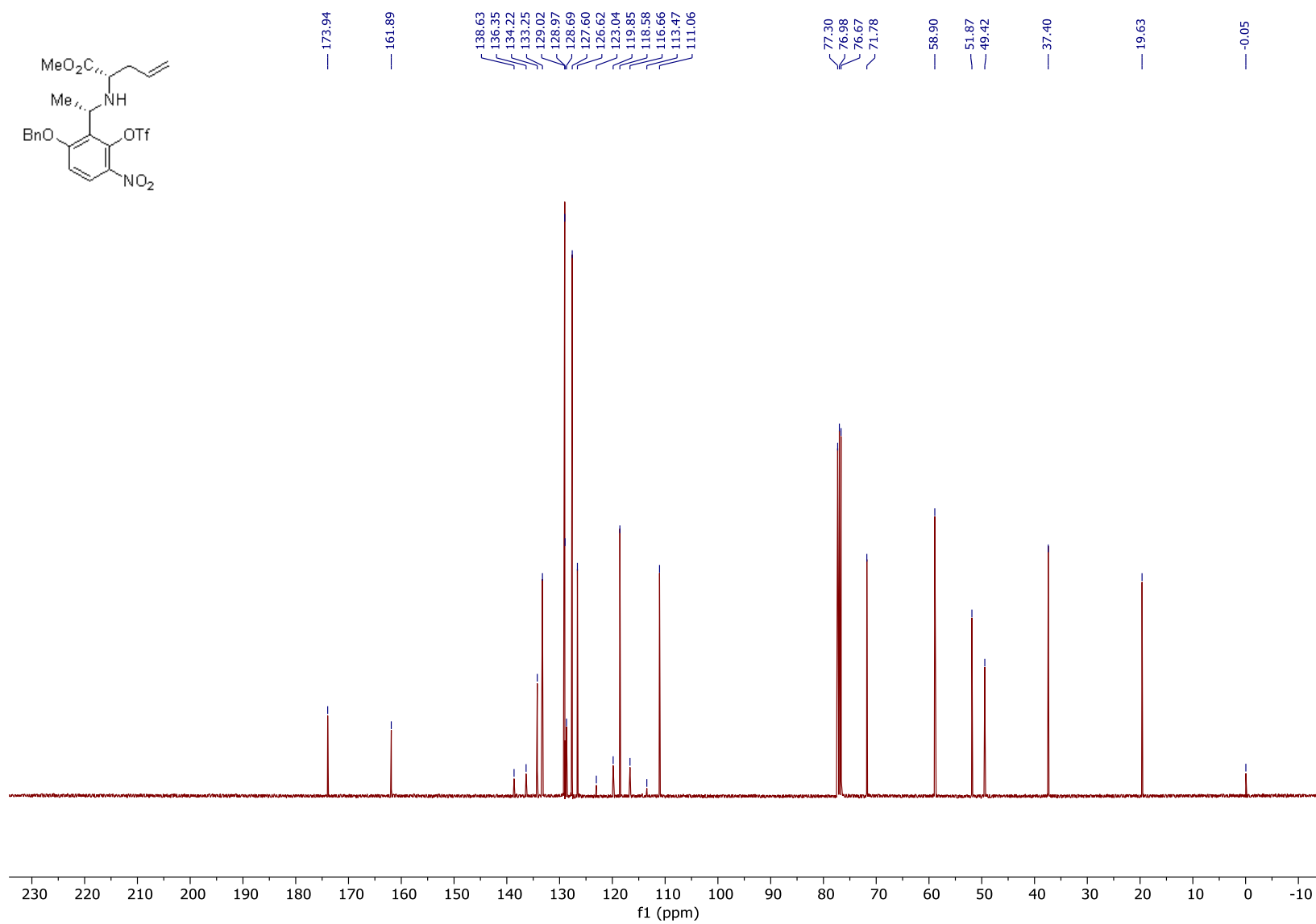


Figure 70: ^{13}C NMR of Compound **155**

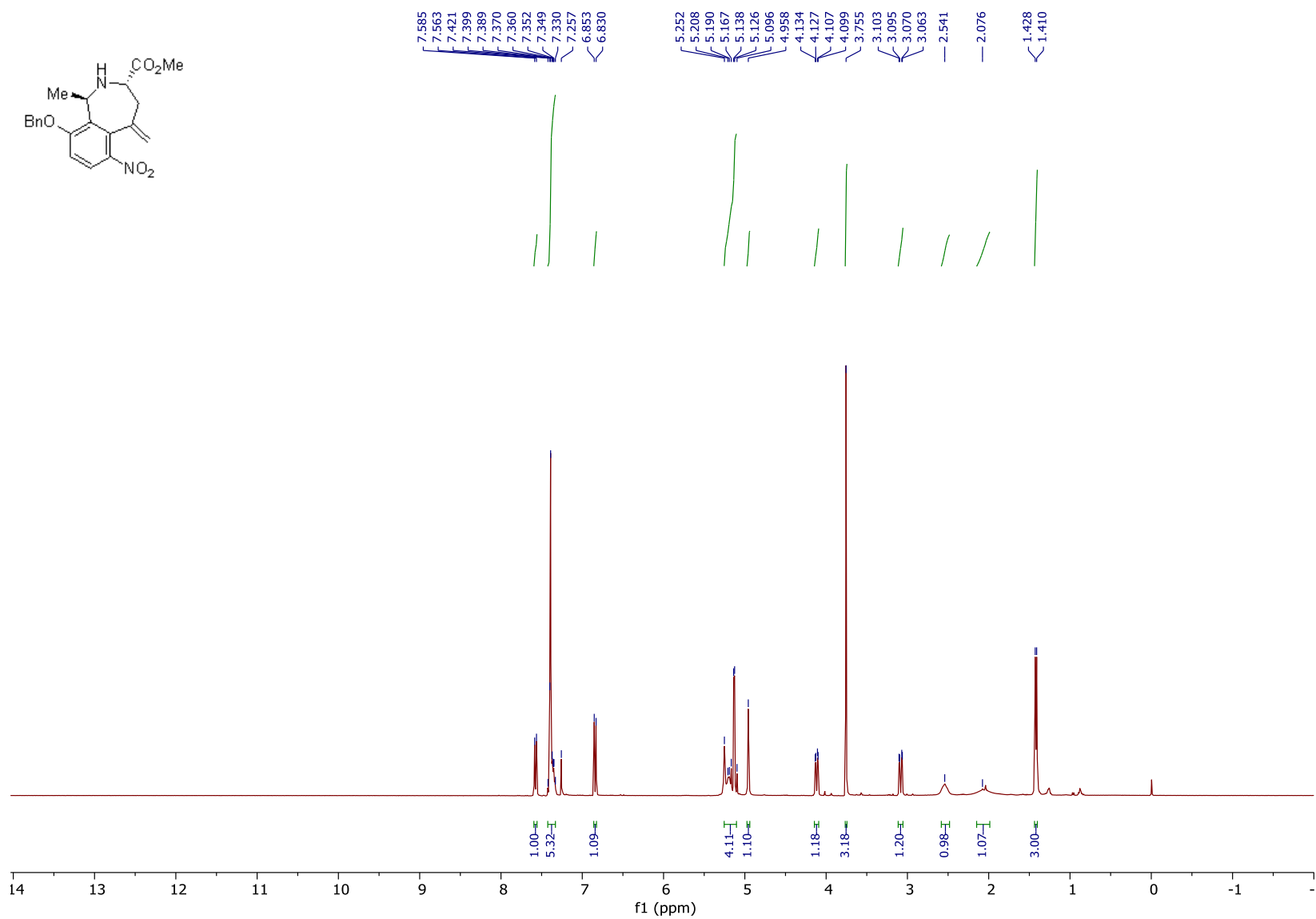


Figure 71: ¹H NMR of Compound 158

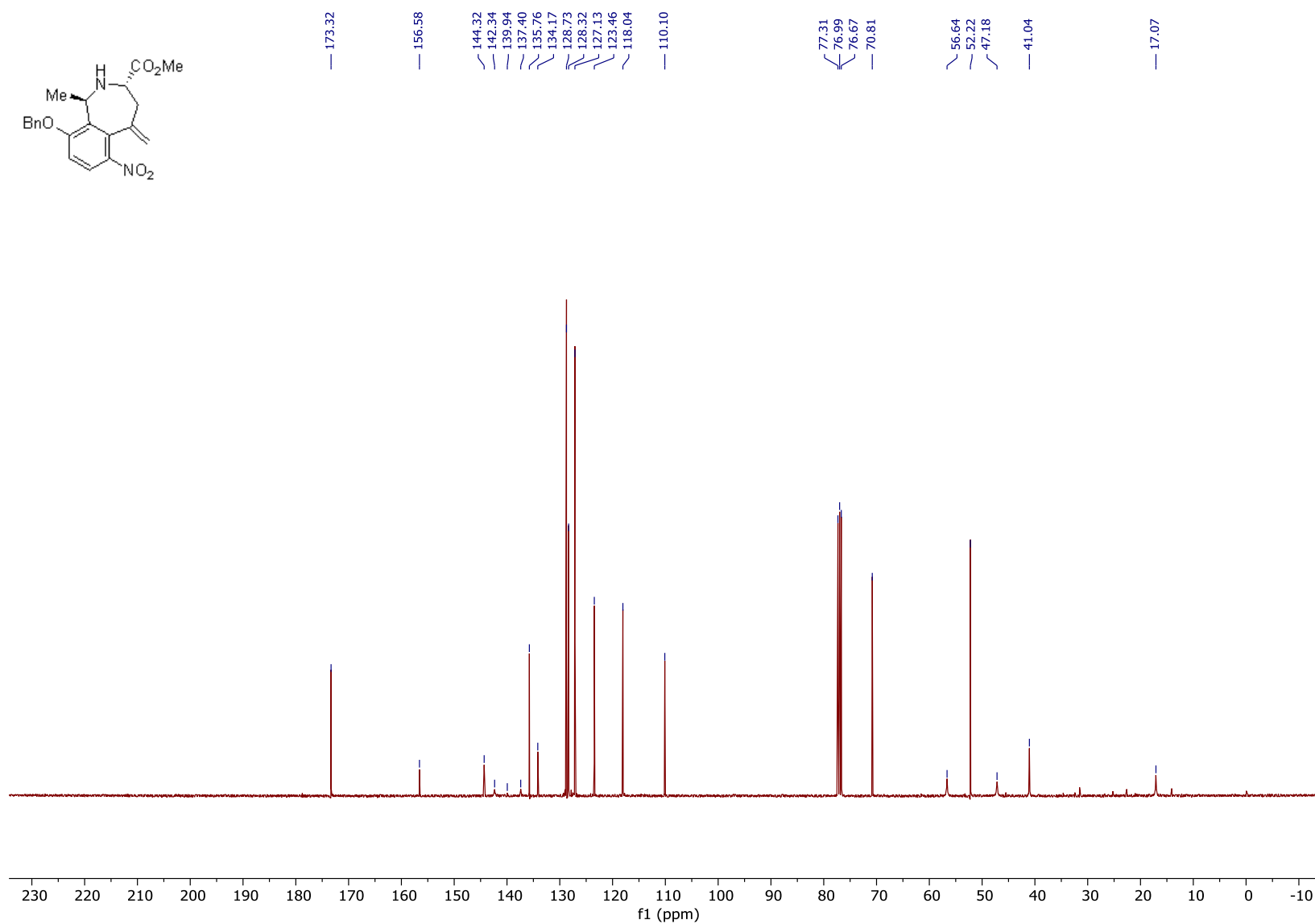


Figure 72: ^{13}C NMR of Compound **158**

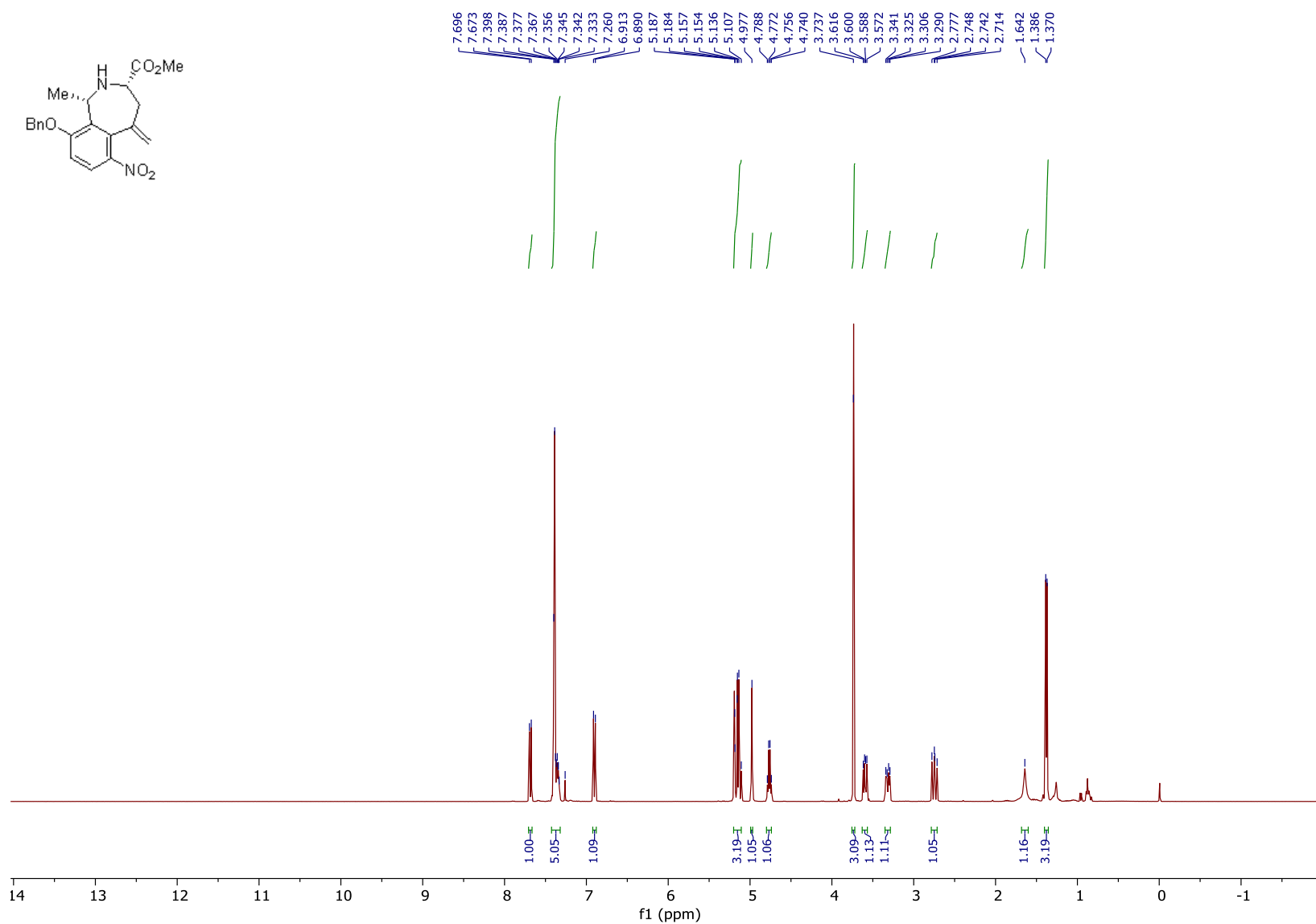


Figure 73: ^1H NMR of Compound **159**

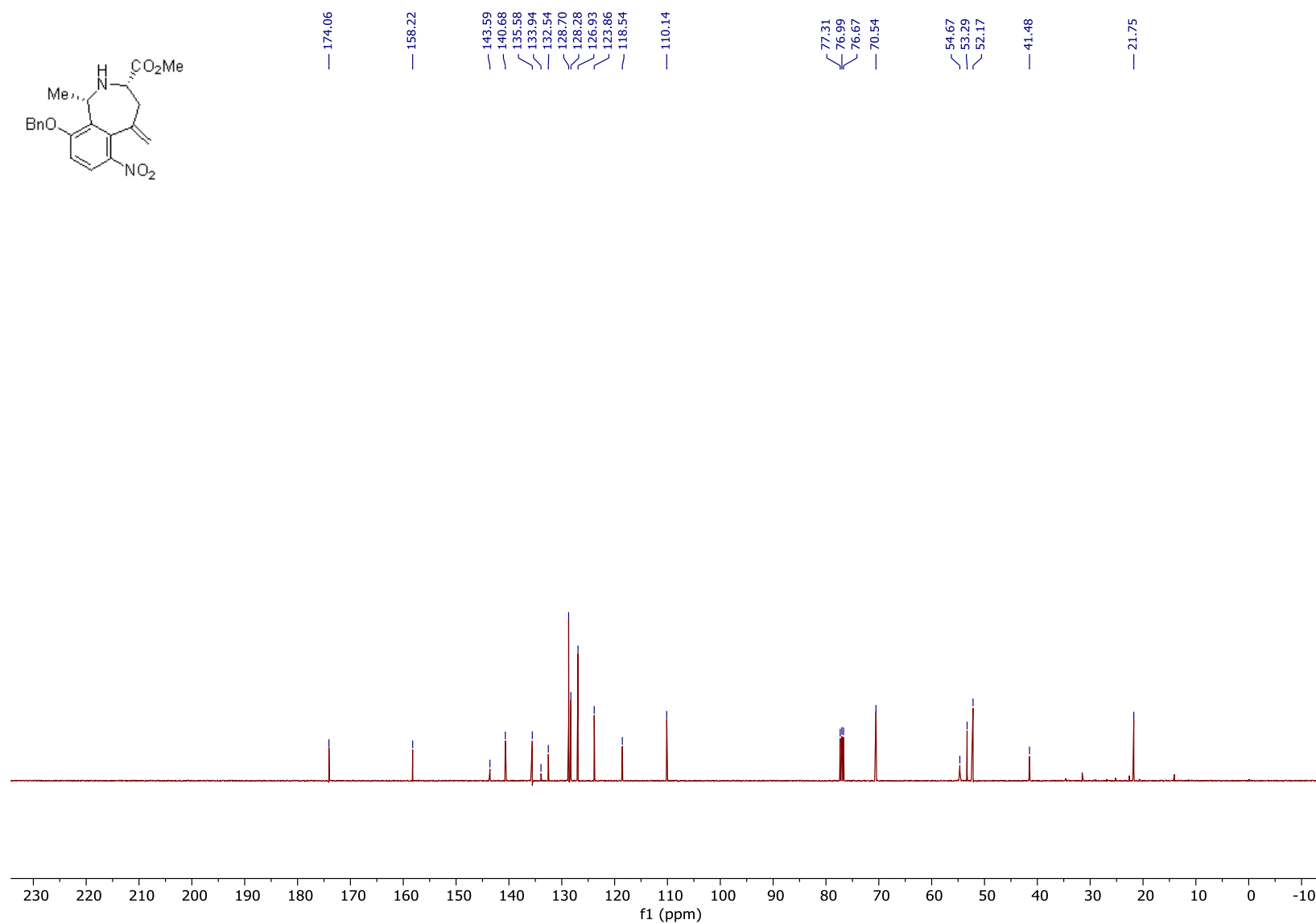


Figure 74: ^{13}C NMR of Compound **159**

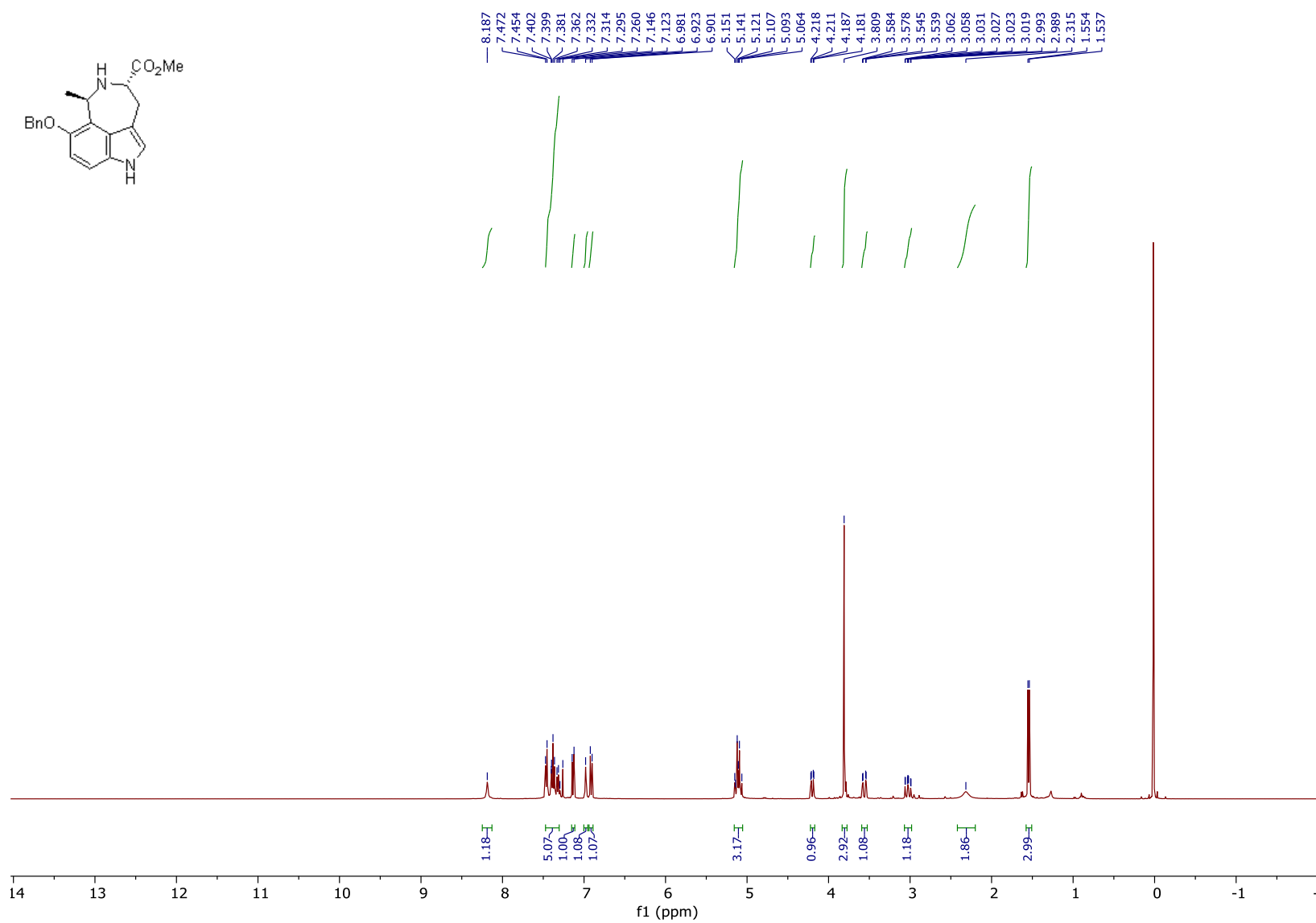


Figure 75: ^1H NMR of Compound **160**

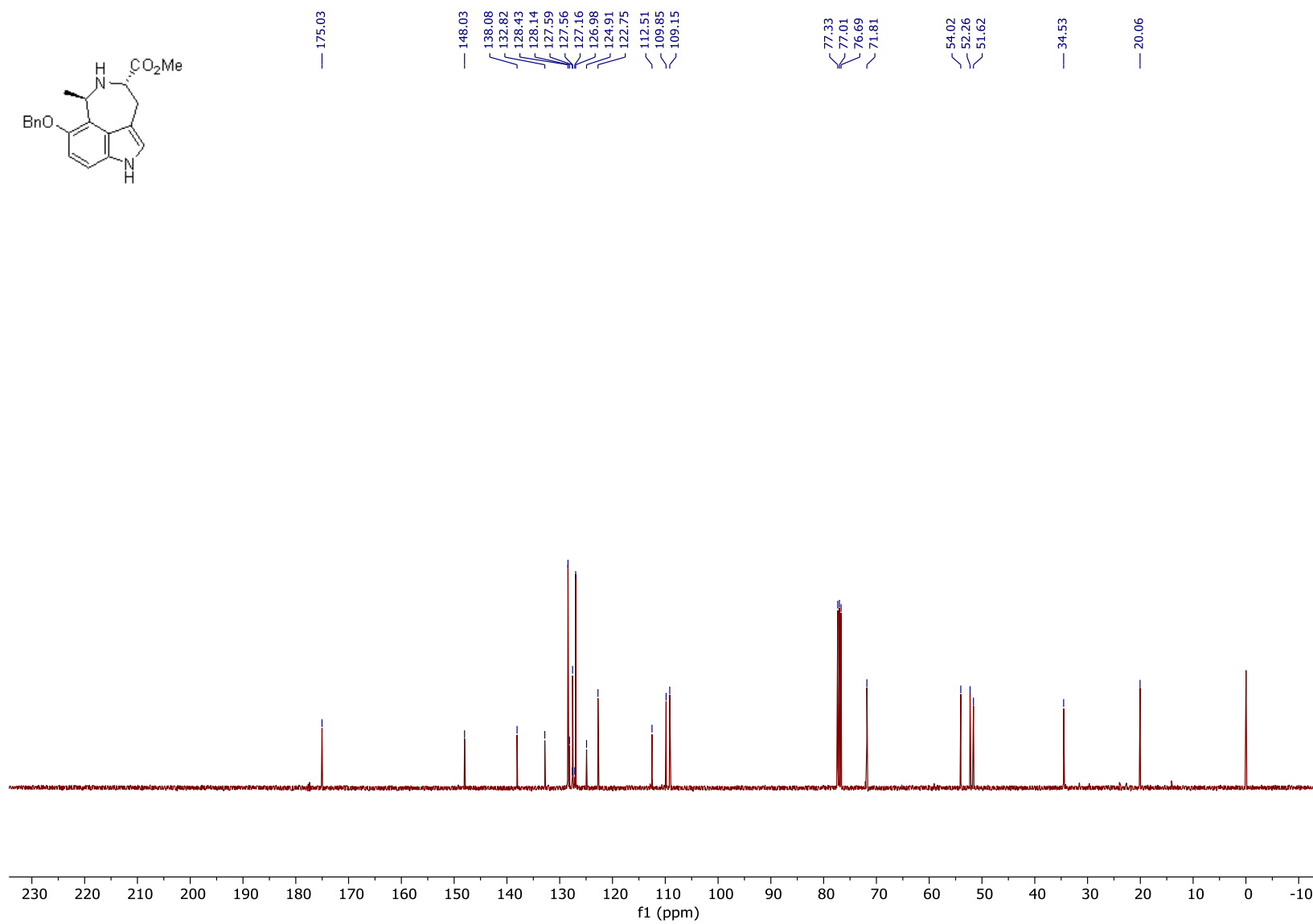


Figure 76: ^{13}C NMR of Compound **160**

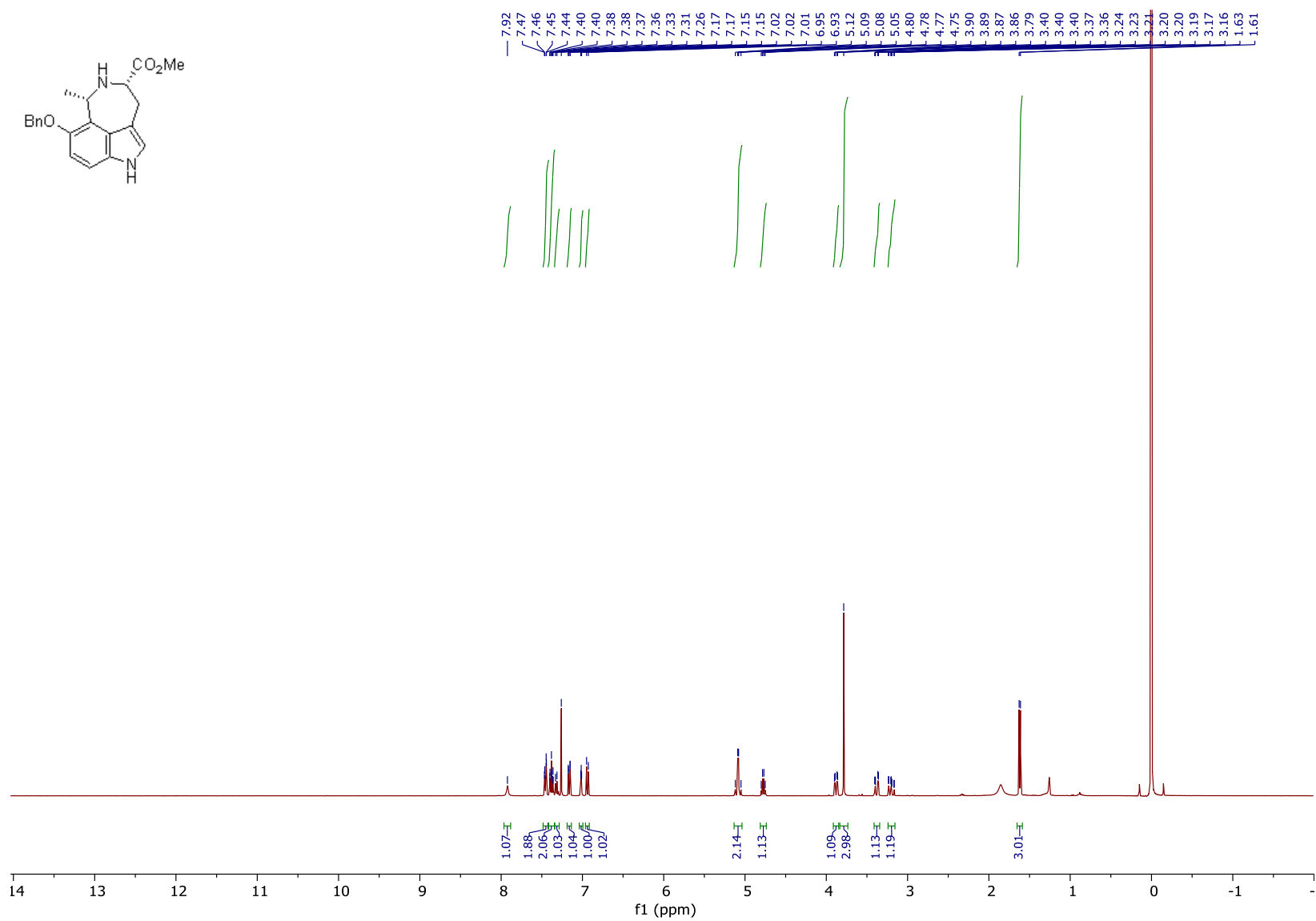


Figure 77: ¹H NMR of Compound 161



Figure 78: ^{13}C NMR of Compound **161**

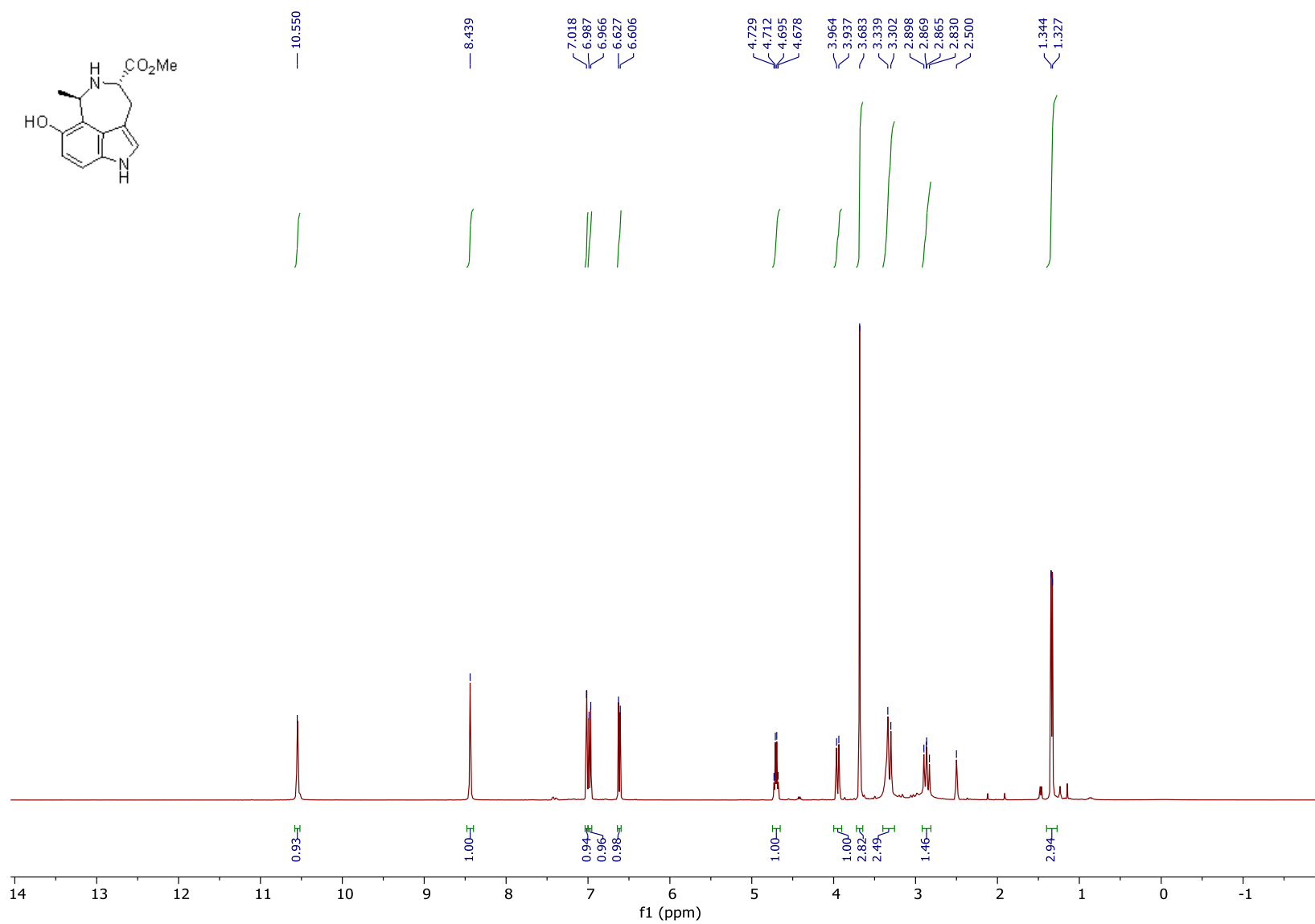


Figure 79: ¹H NMR of Compound 164

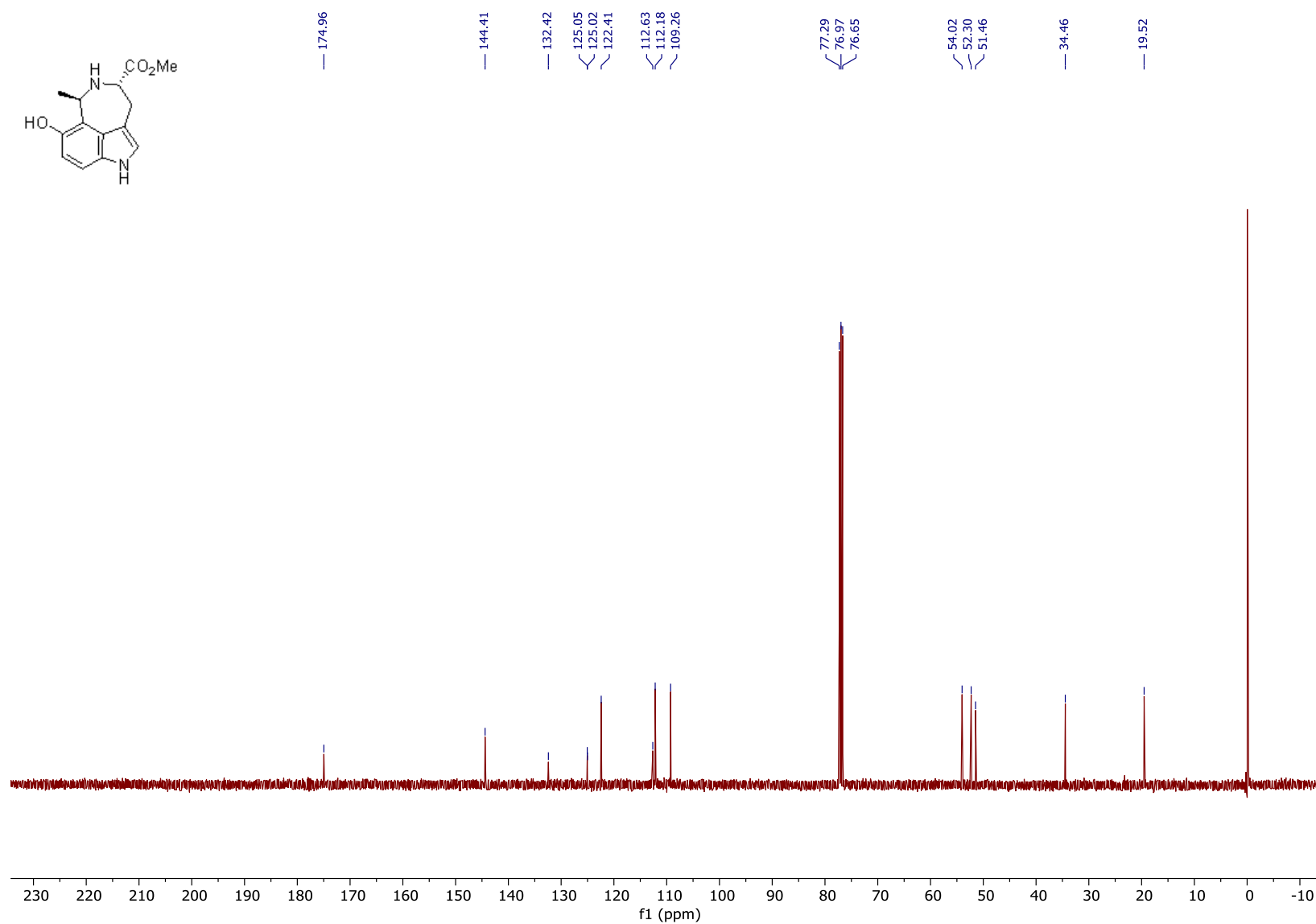


Figure 80: ^{13}C NMR of Compound **164**

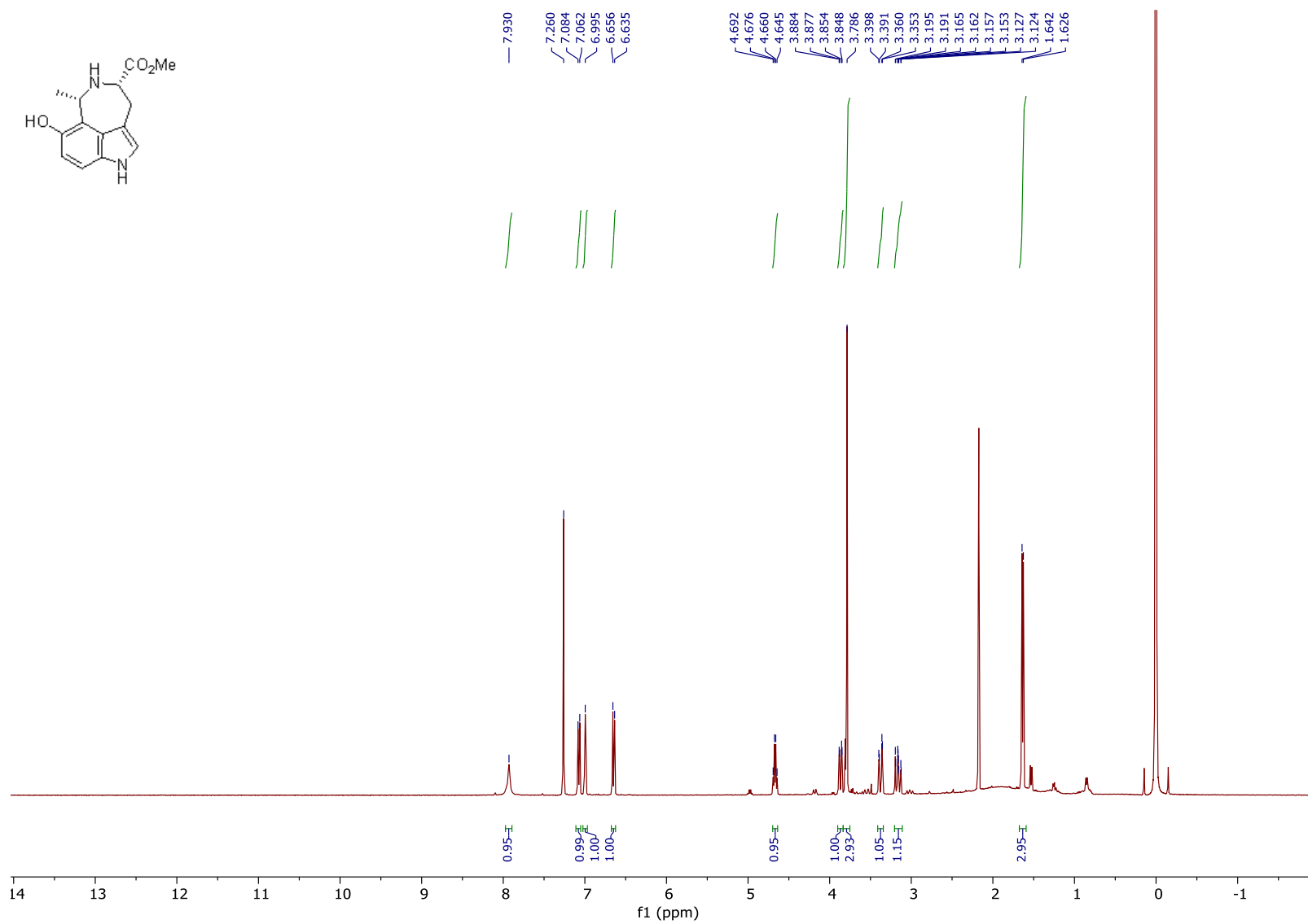


Figure 81: ¹H NMR of Compound **165**

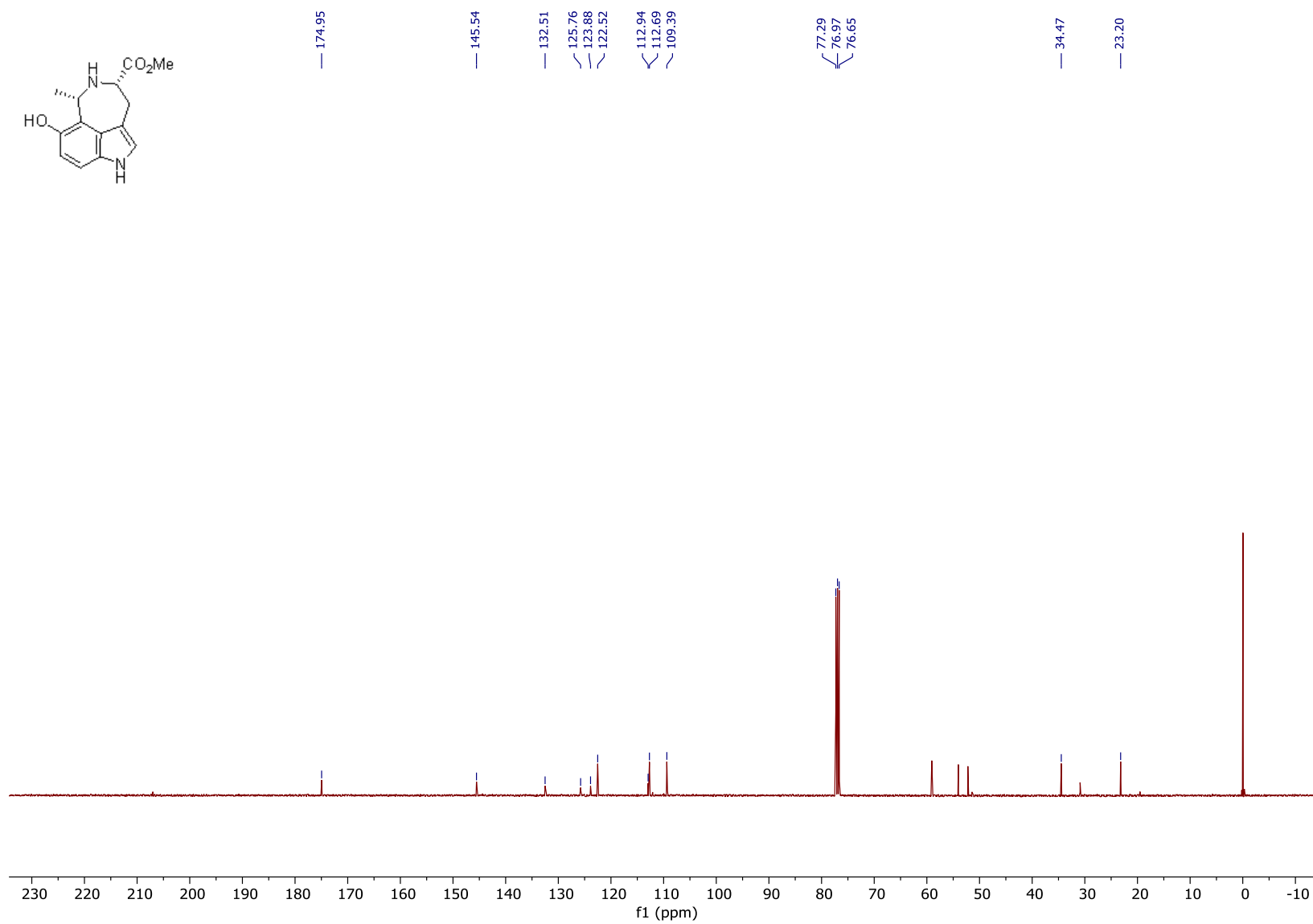


Figure 82: ^{13}C NMR of Compound **165**

¹H and ¹³C NMR for Chapter 4: Aurantioclavine

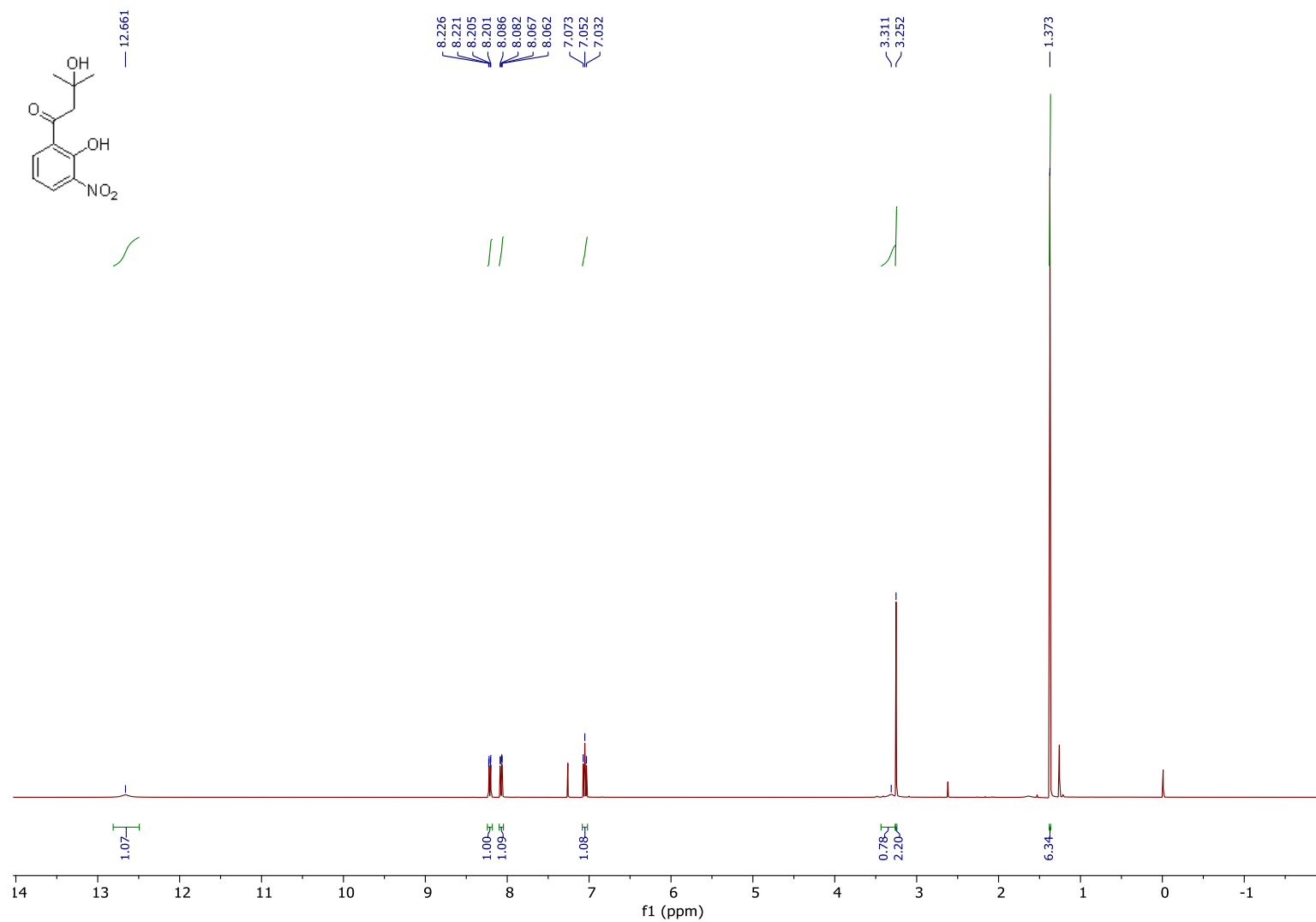


Figure 83: ¹H NMR of Compound 200

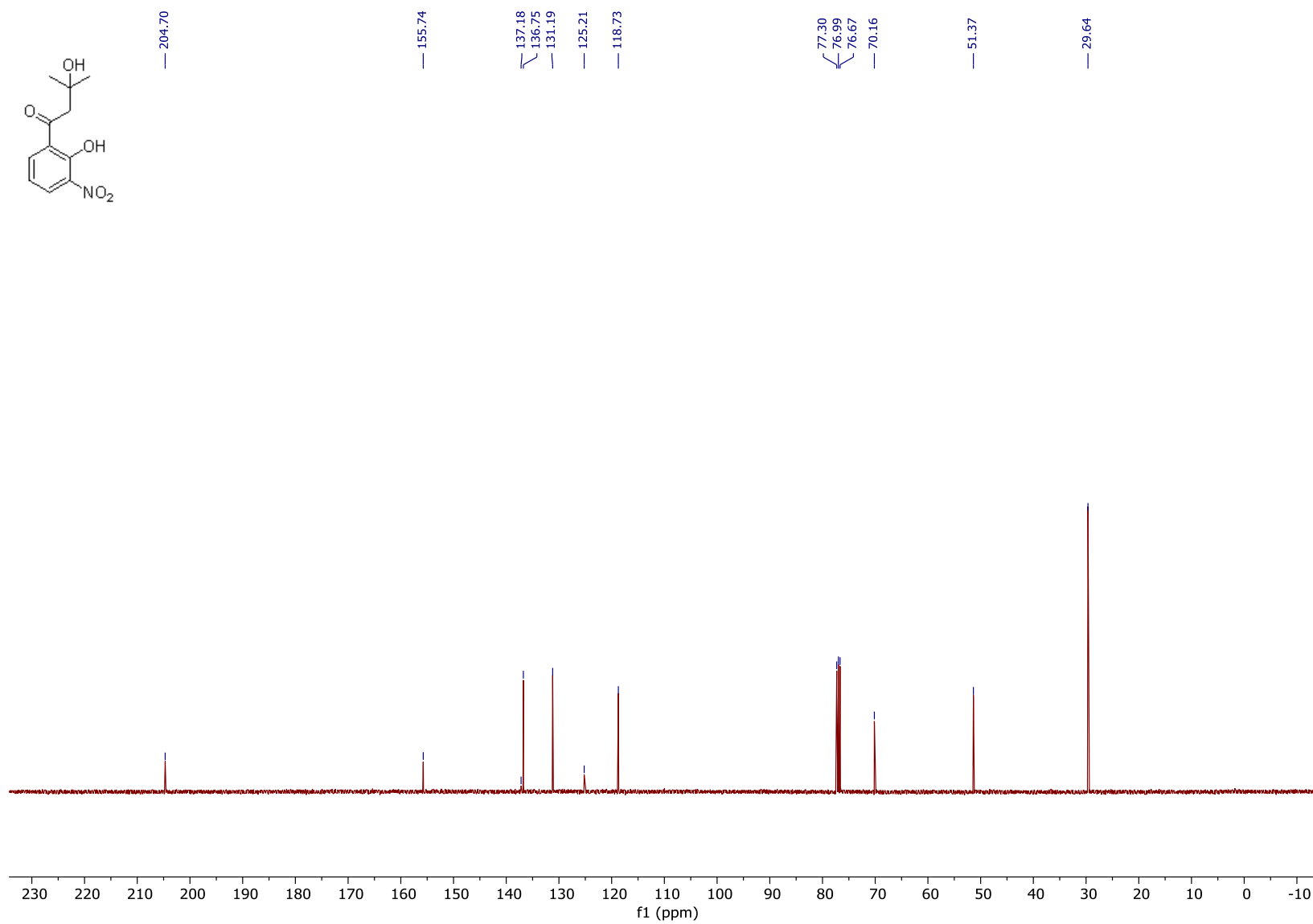


Figure 84: ¹³C NMR of Compound **200**

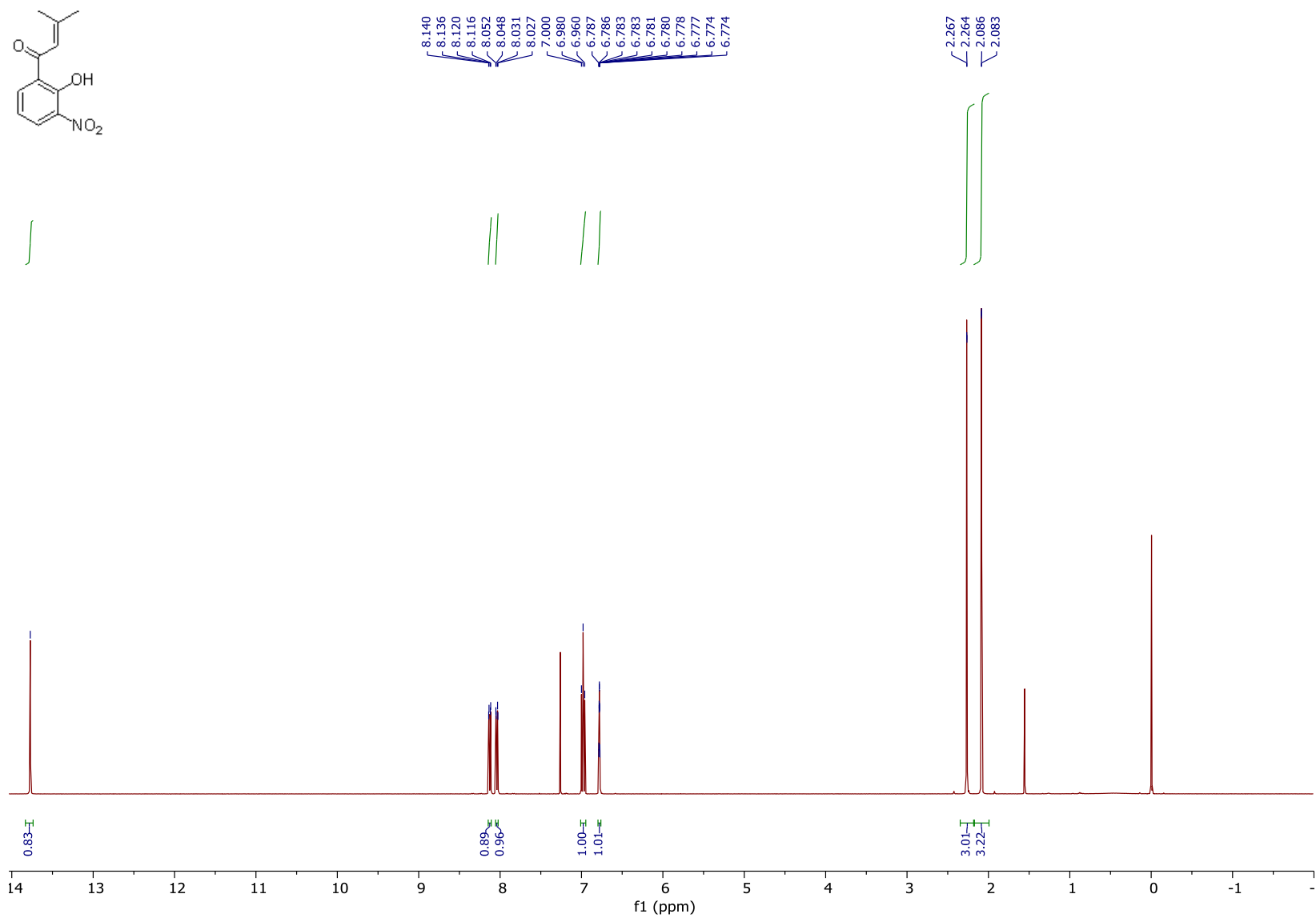


Figure 85: ^1H NMR of Compound **201**

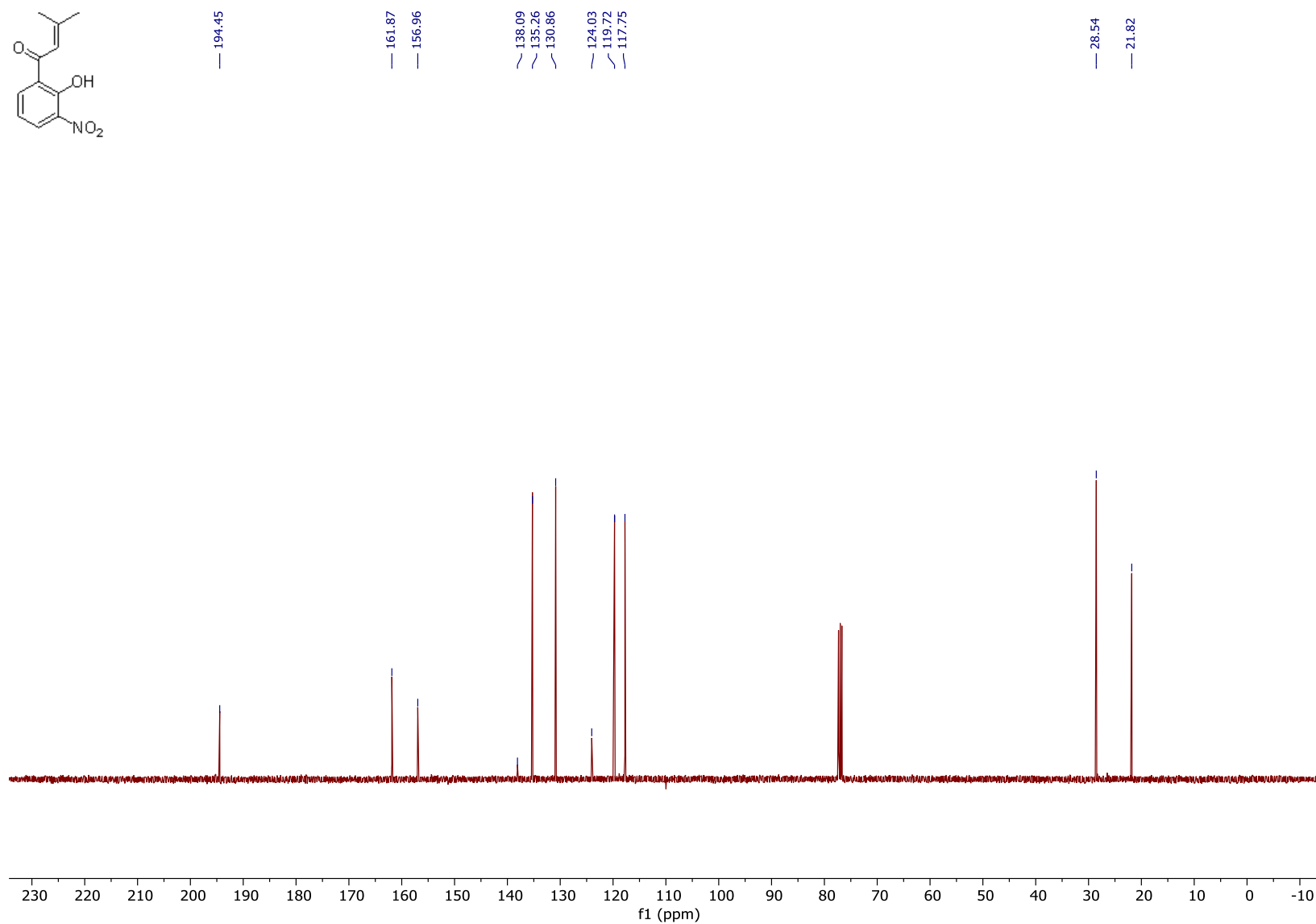


Figure 86: ^{13}C NMR of Compound **201**

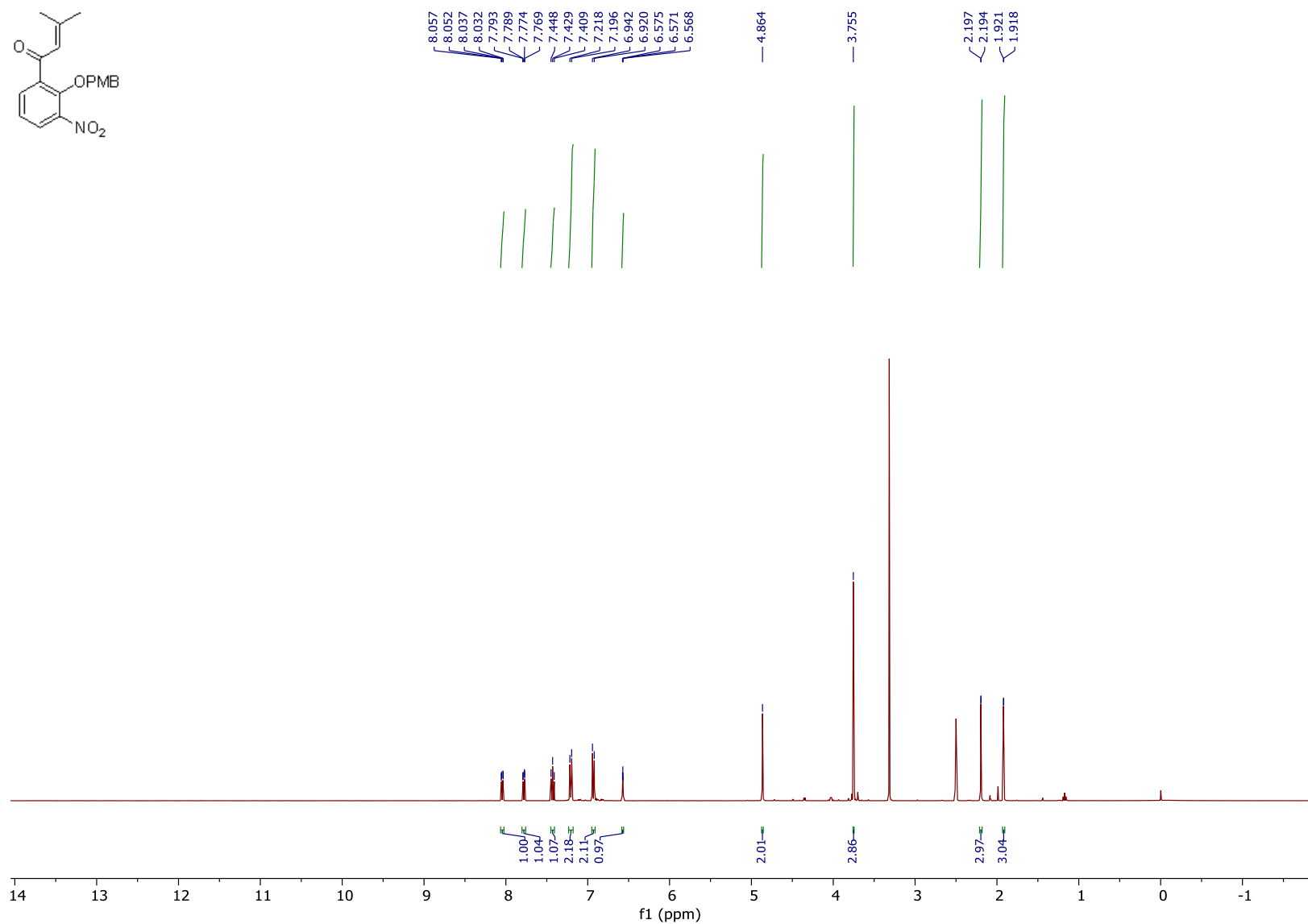


Figure 87: ^1H NMR of Compound **203**

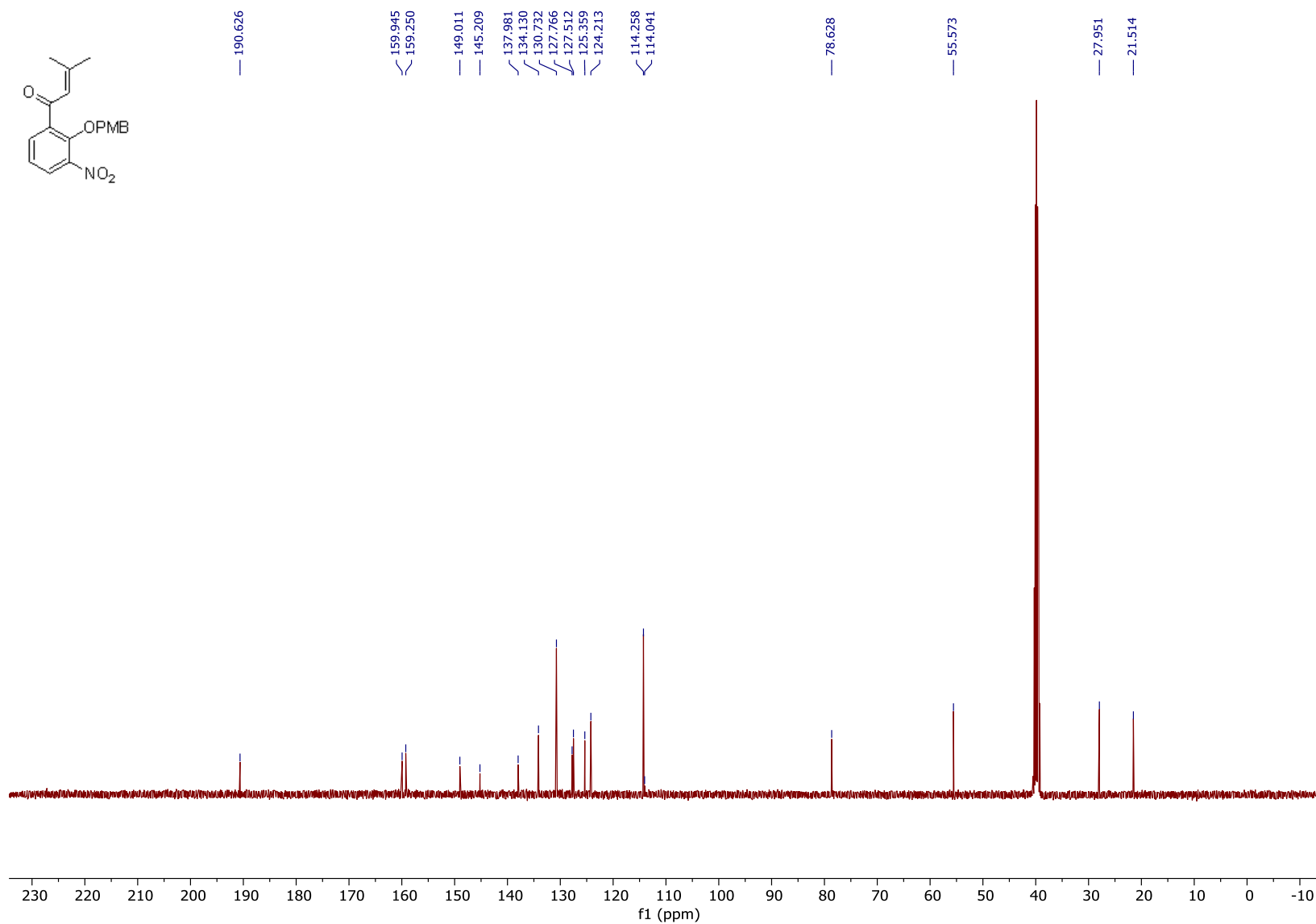


Figure 88: ^{13}C NMR of Compound **203**

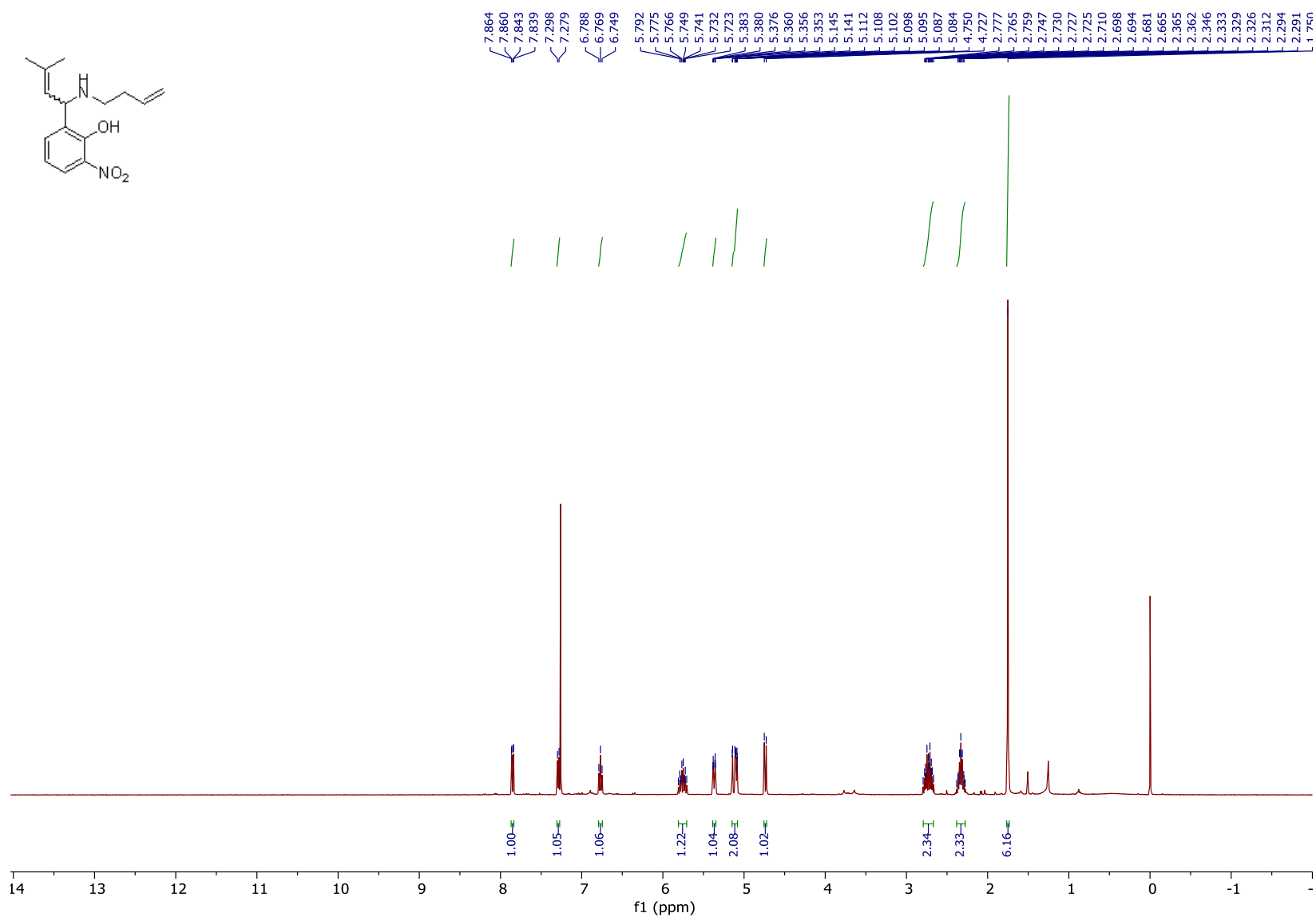


Figure 89: ^1H NMR of Compound **205**

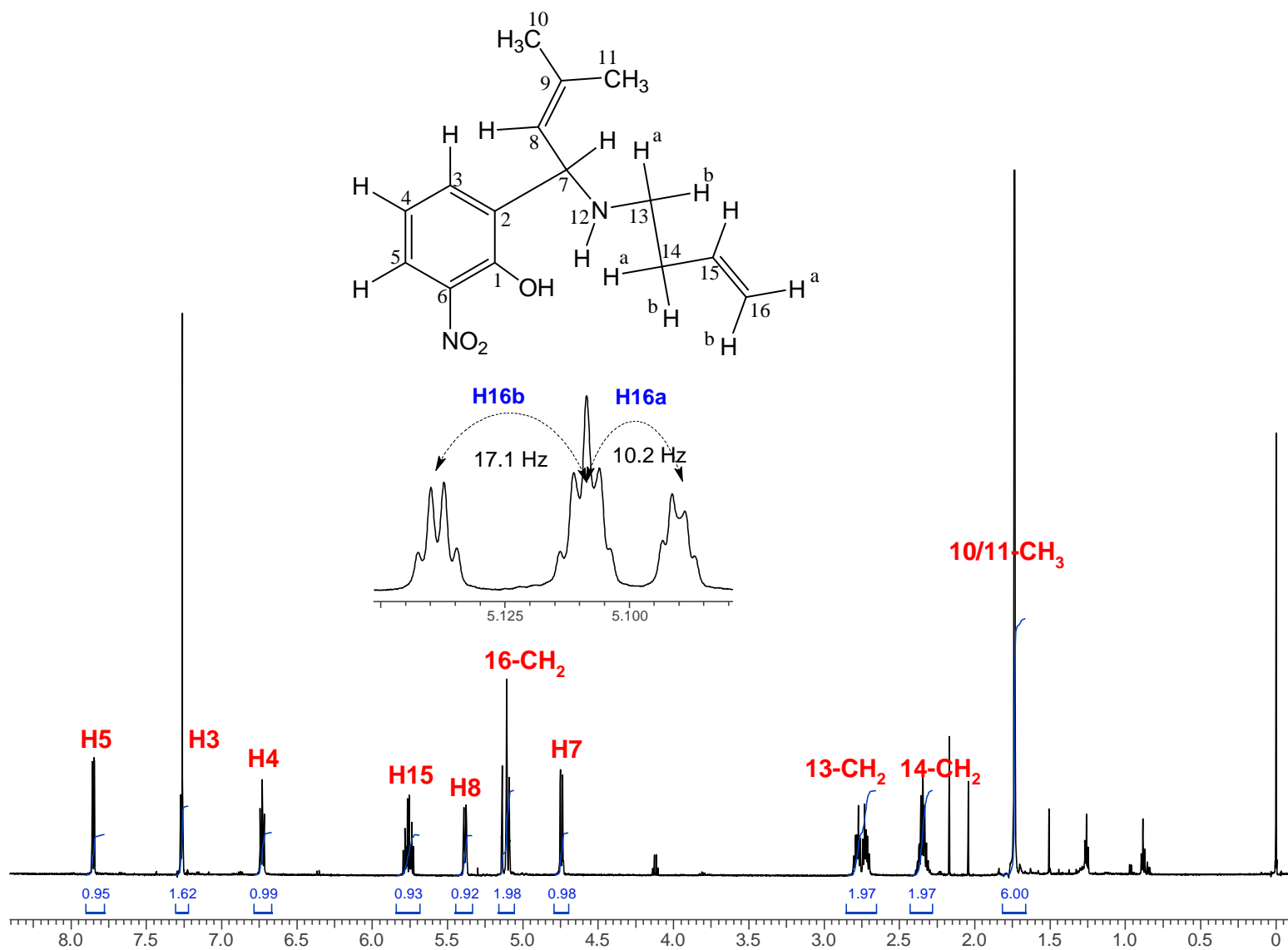


Figure 90: ^1H NMR of Compound **205**

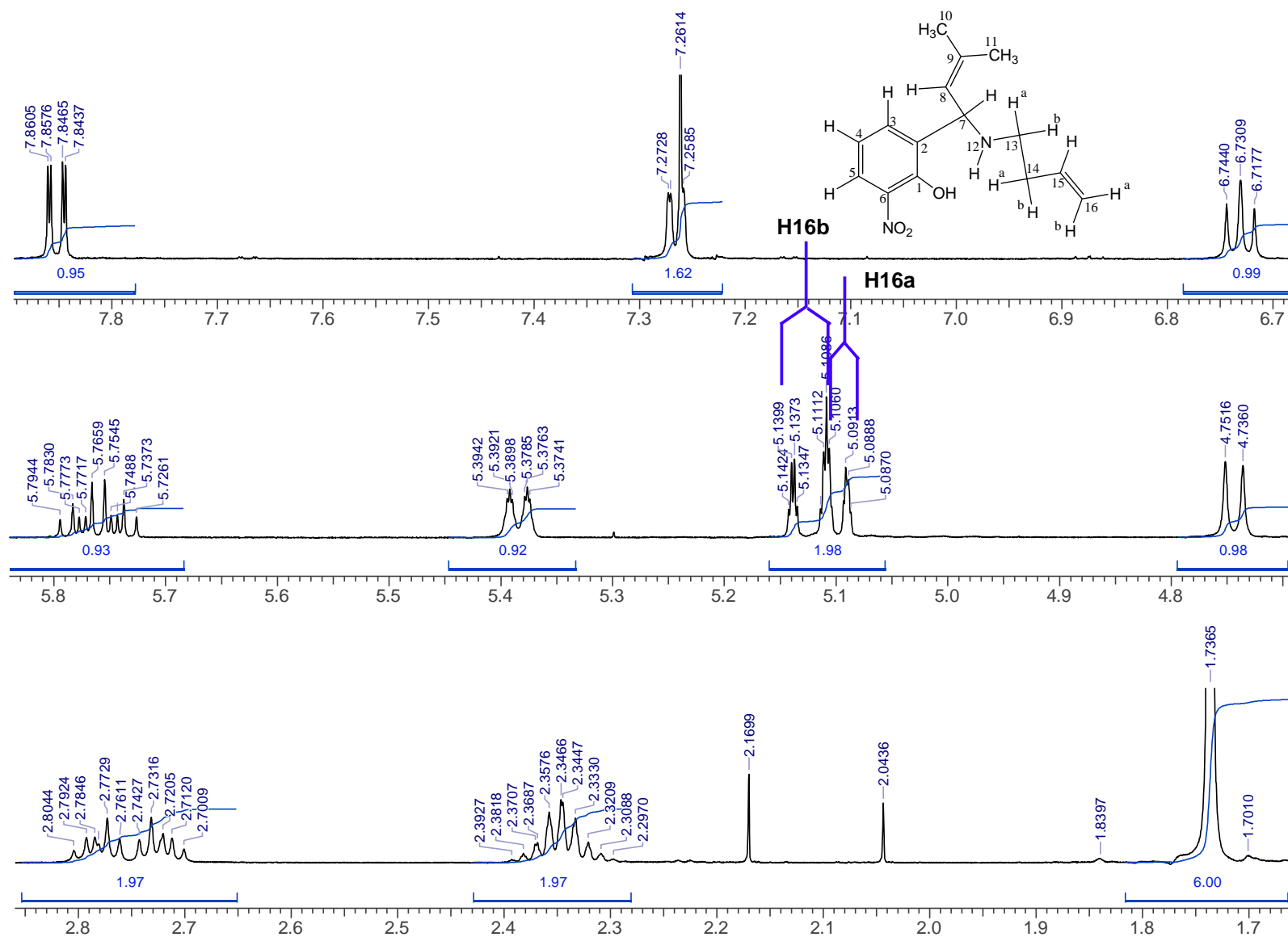


Figure 91: ¹H NMR of Compound **205**

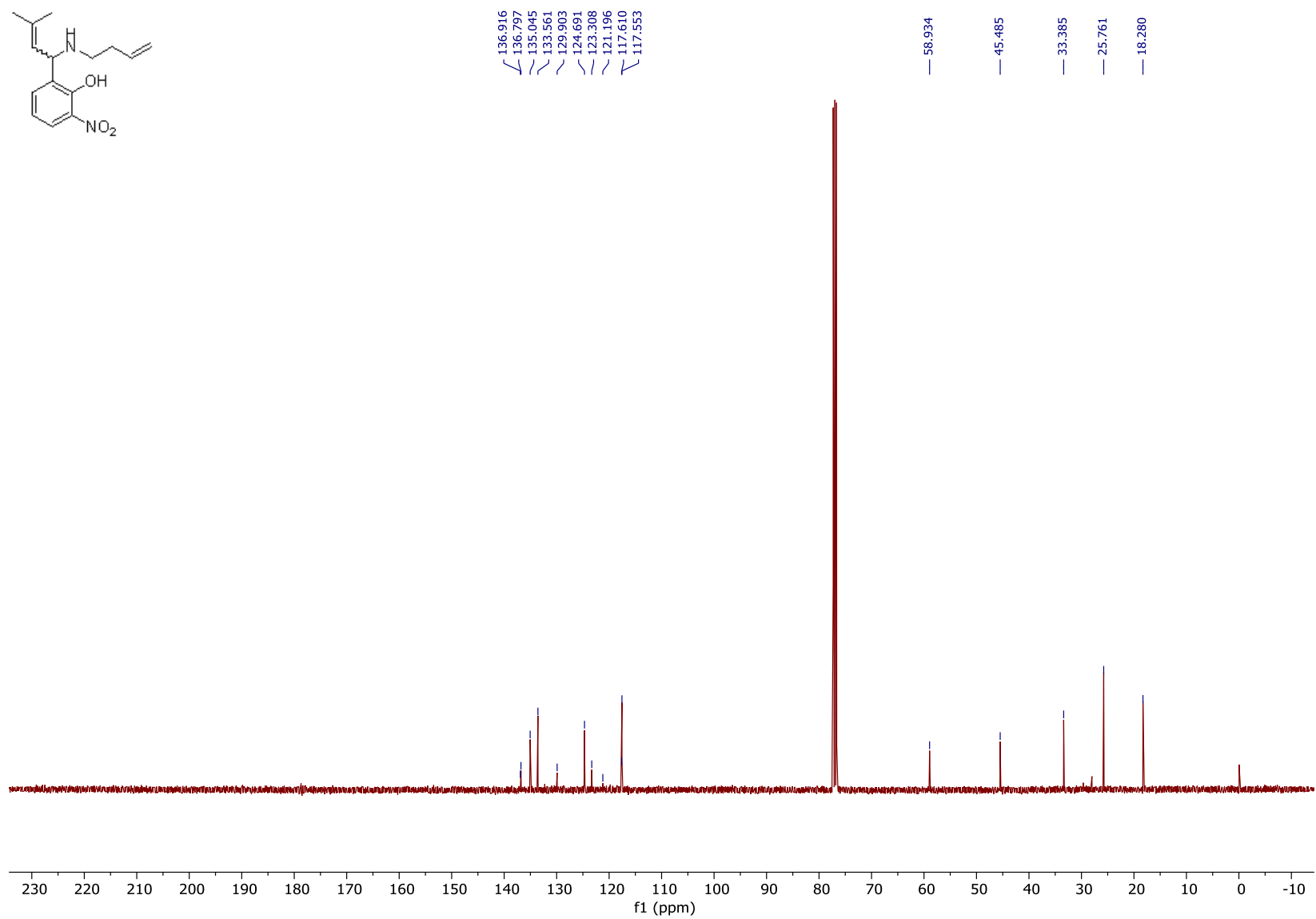


Figure 92: ¹³C NMR of Compound **205**

gCOSY

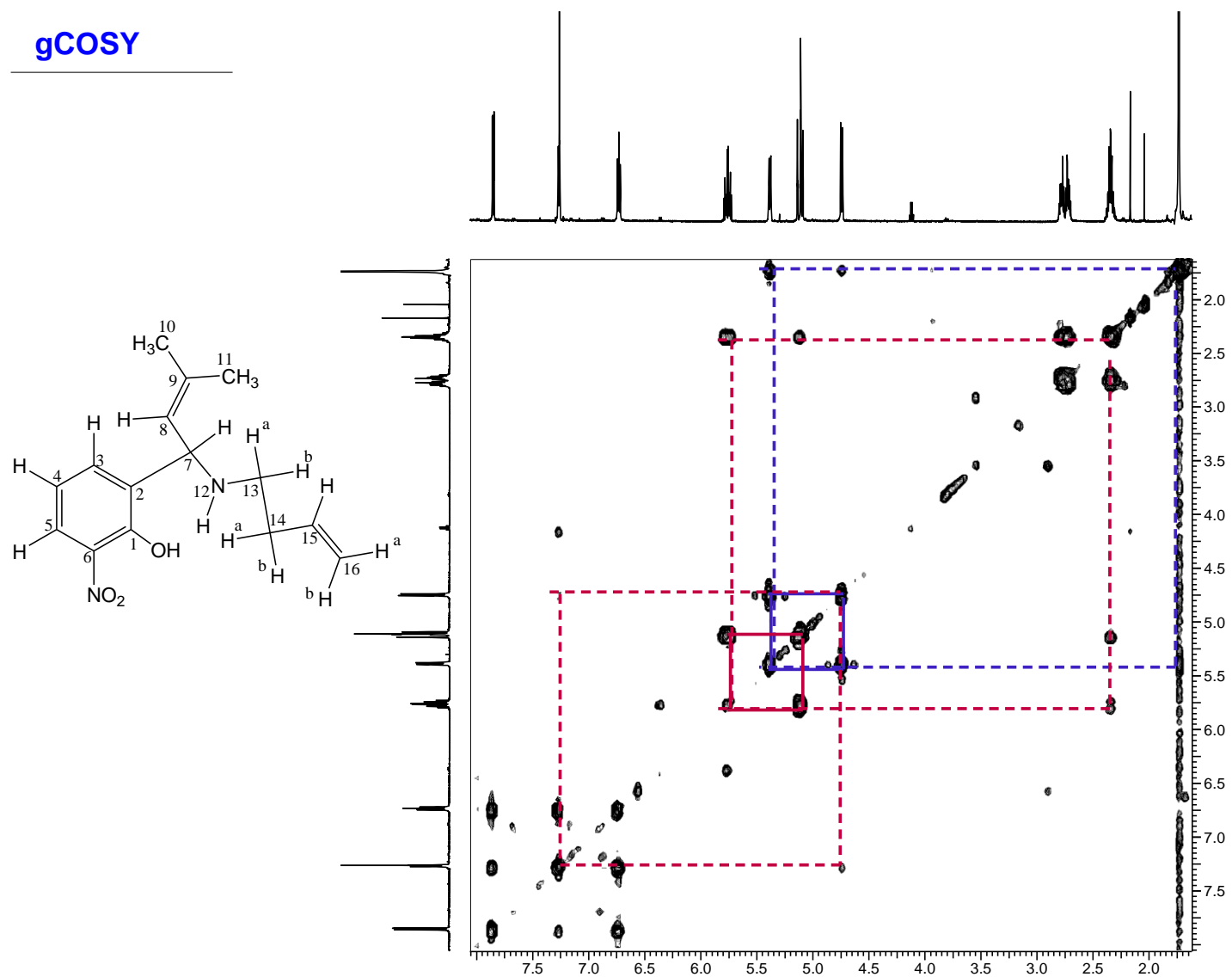


Figure 93: COSY of Compound 205

gHSQCAD

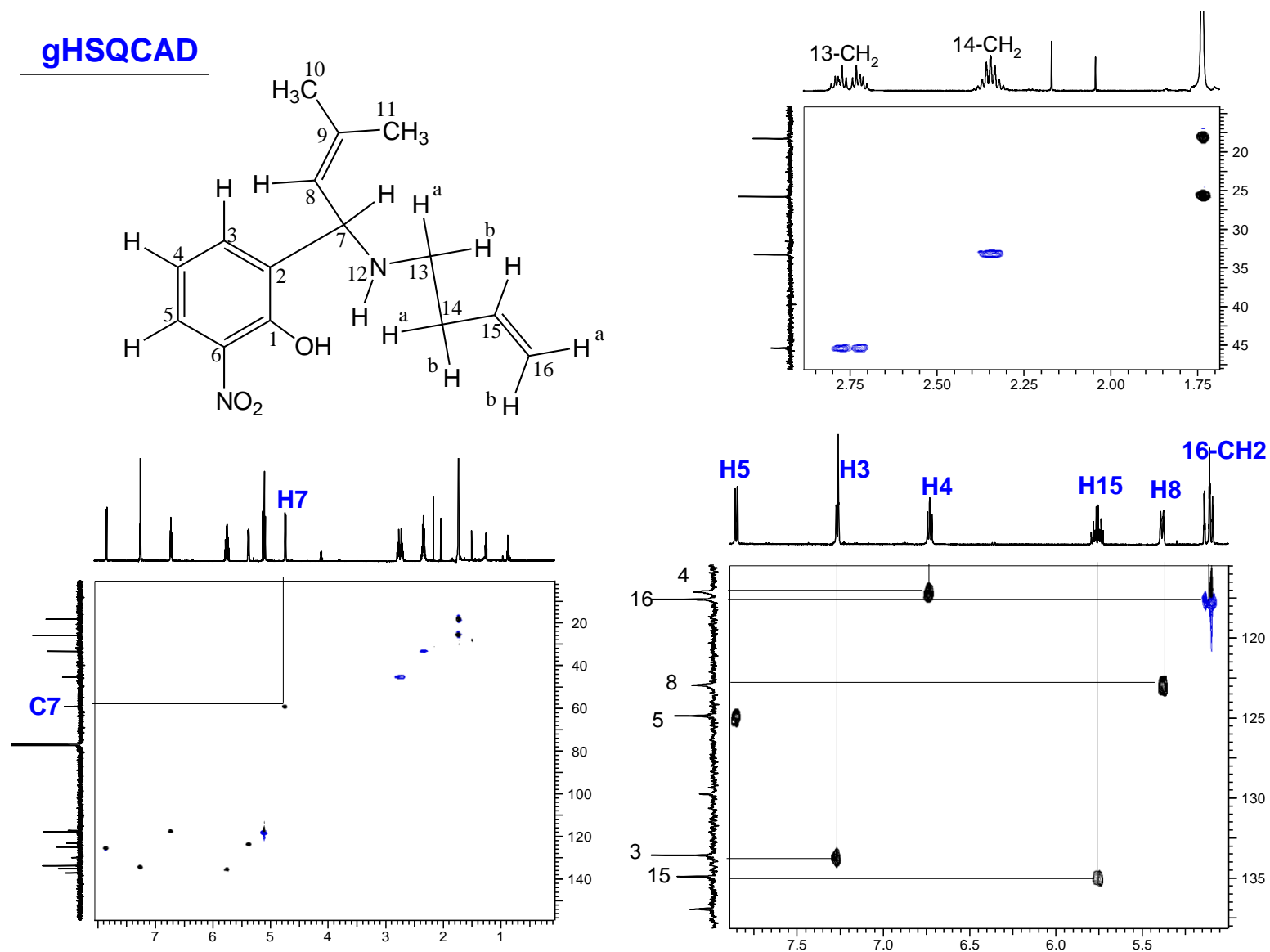


Figure 94: HSQC of Compound 205

DPFGSENOE

subspectra

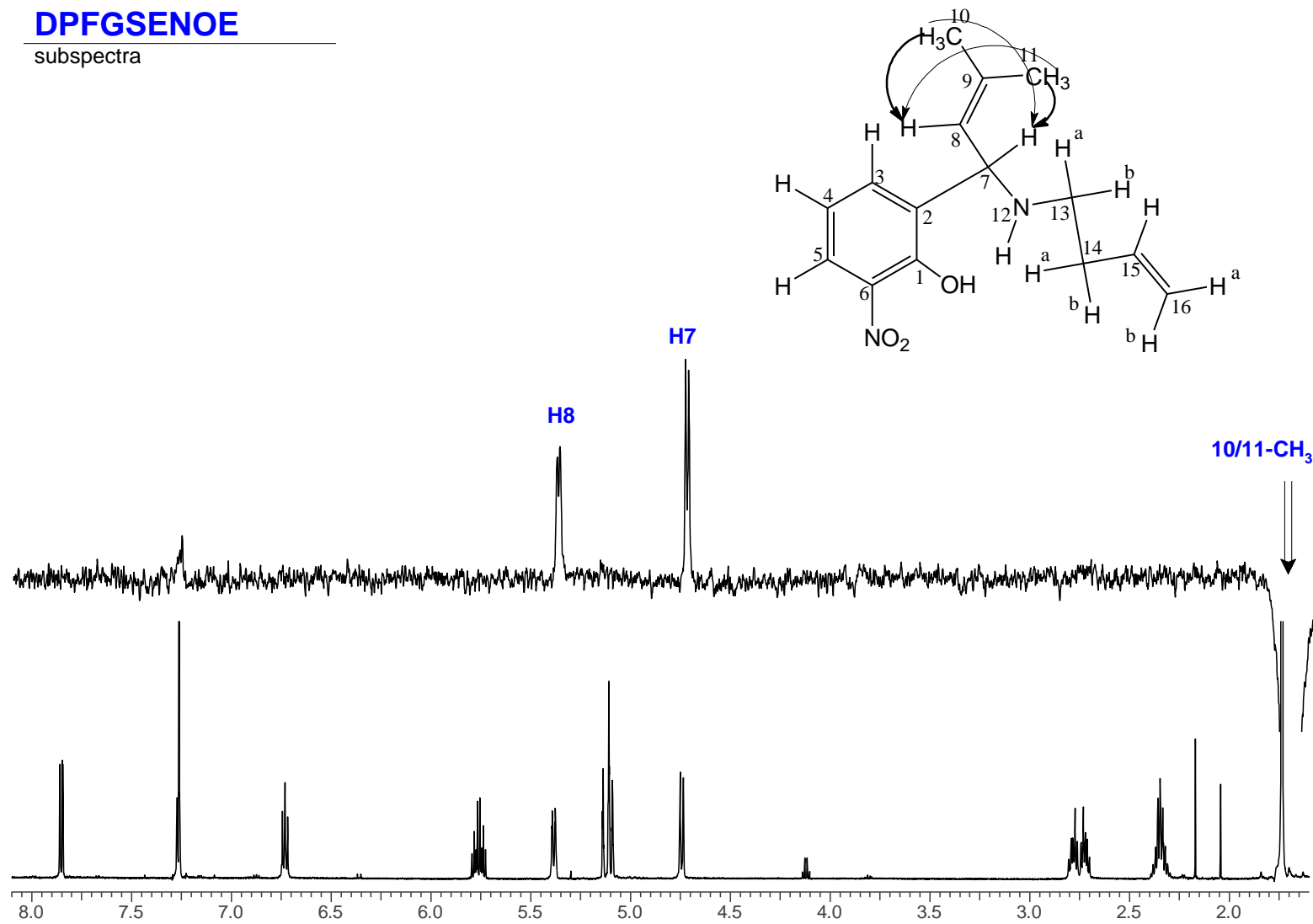


Figure 95: NOE of Compound 205

DPFGSENOE

subspectra

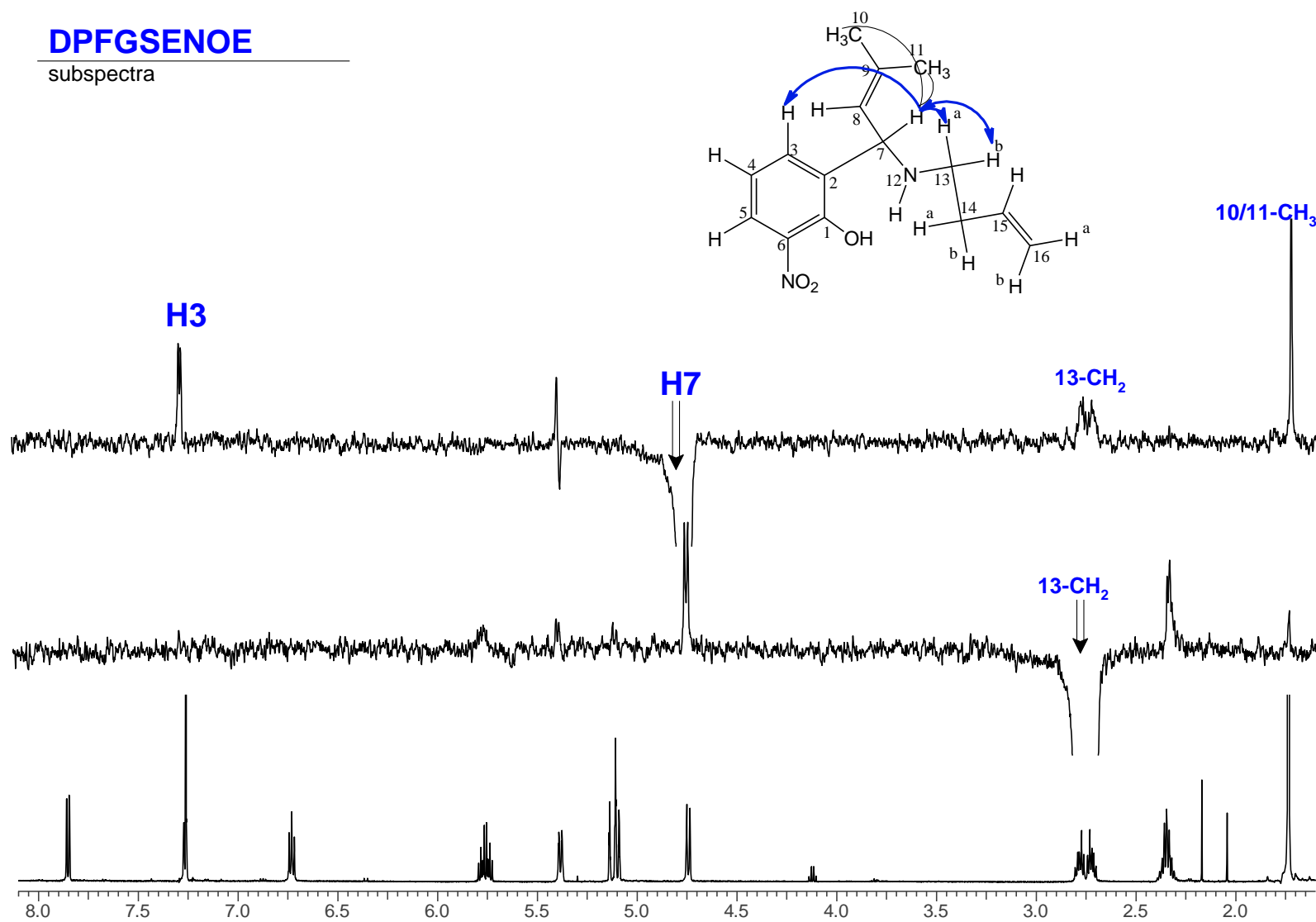


Figure 96: NOE of Compound 205

DPFGSENOE

subspectra

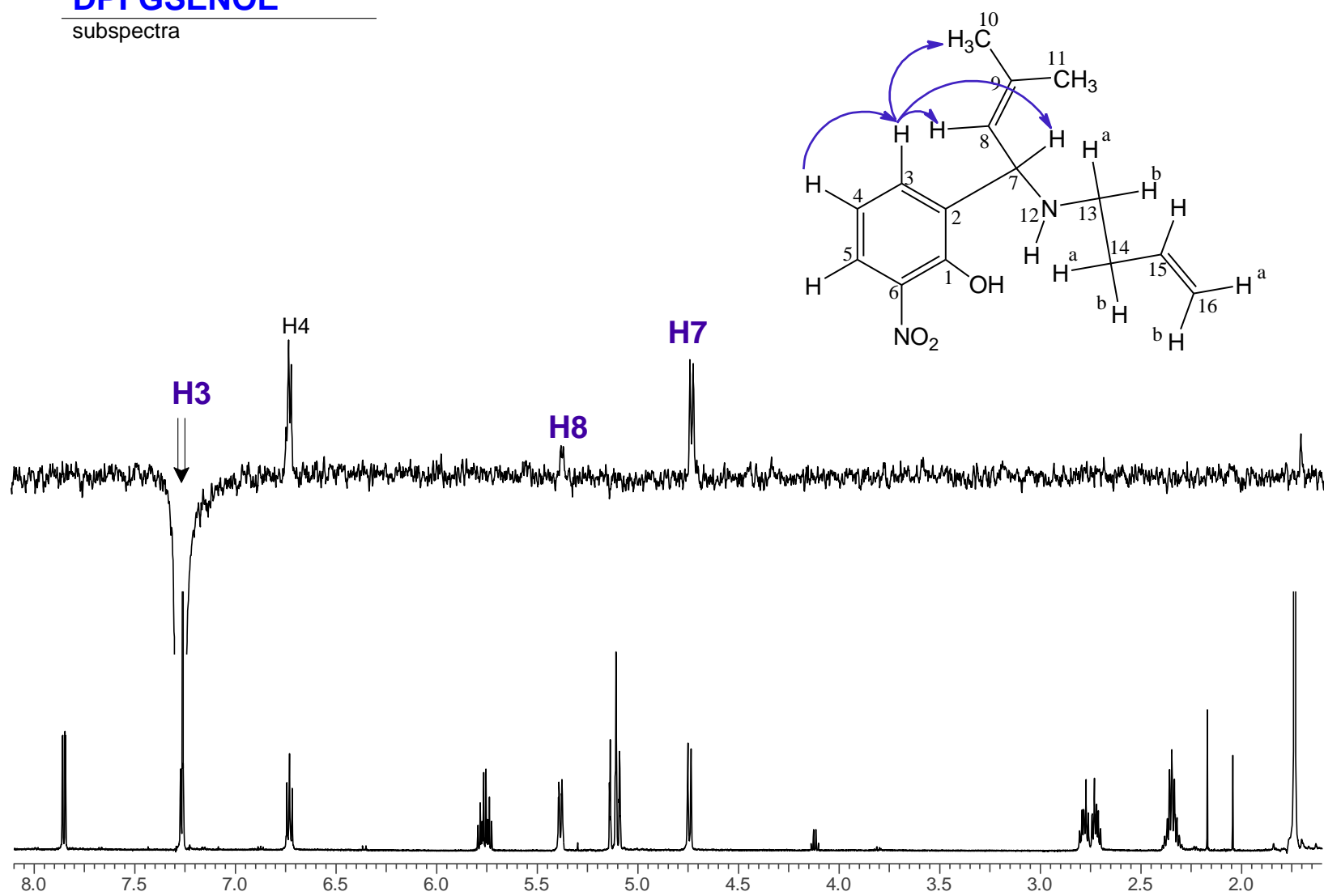


Figure 97: NOE of Compound **205**

gHMBCAD

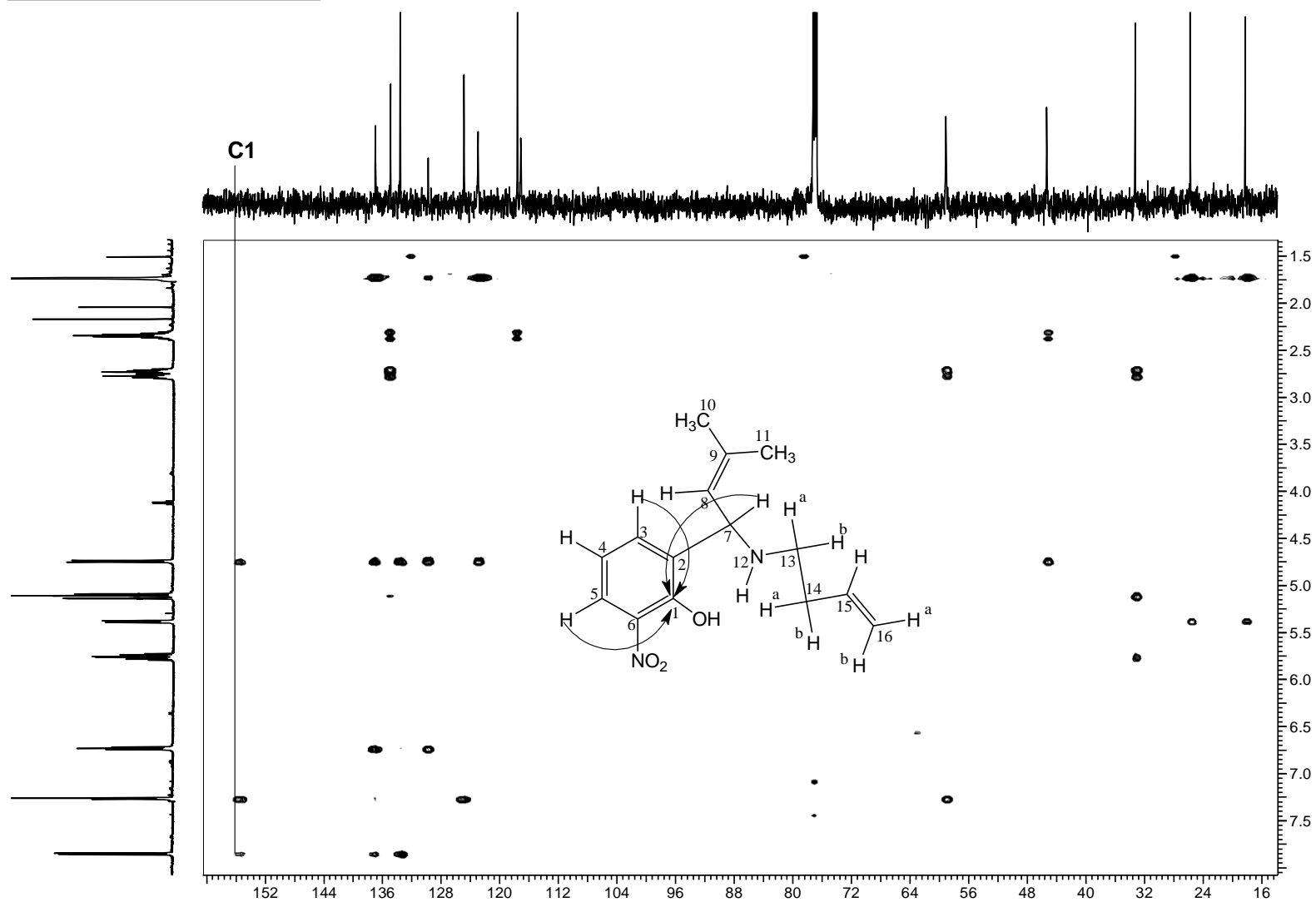


Figure 98: HMBC of Compound **205**

gHMBCAD

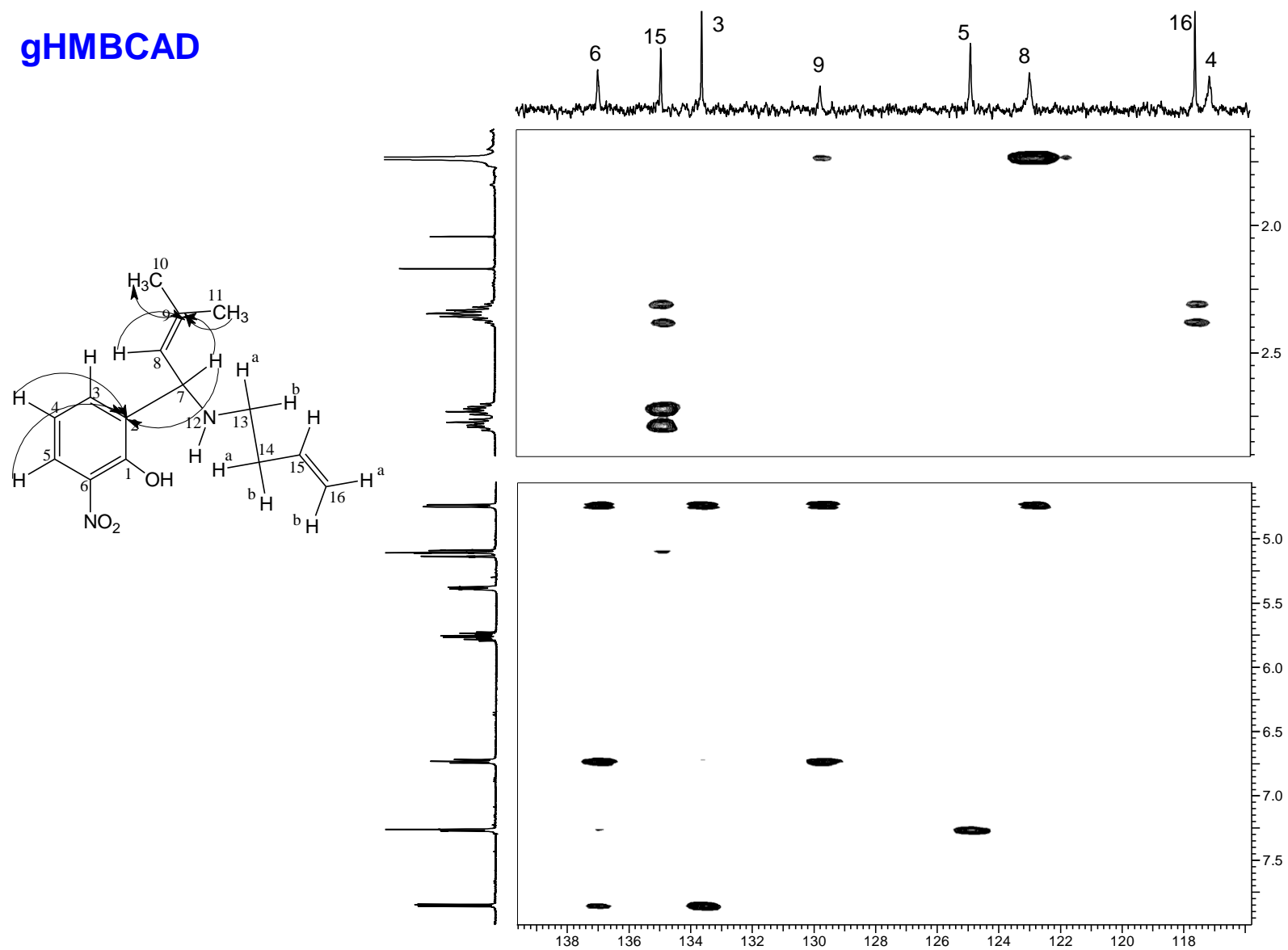


Figure 99: HMBC of Compound **205**

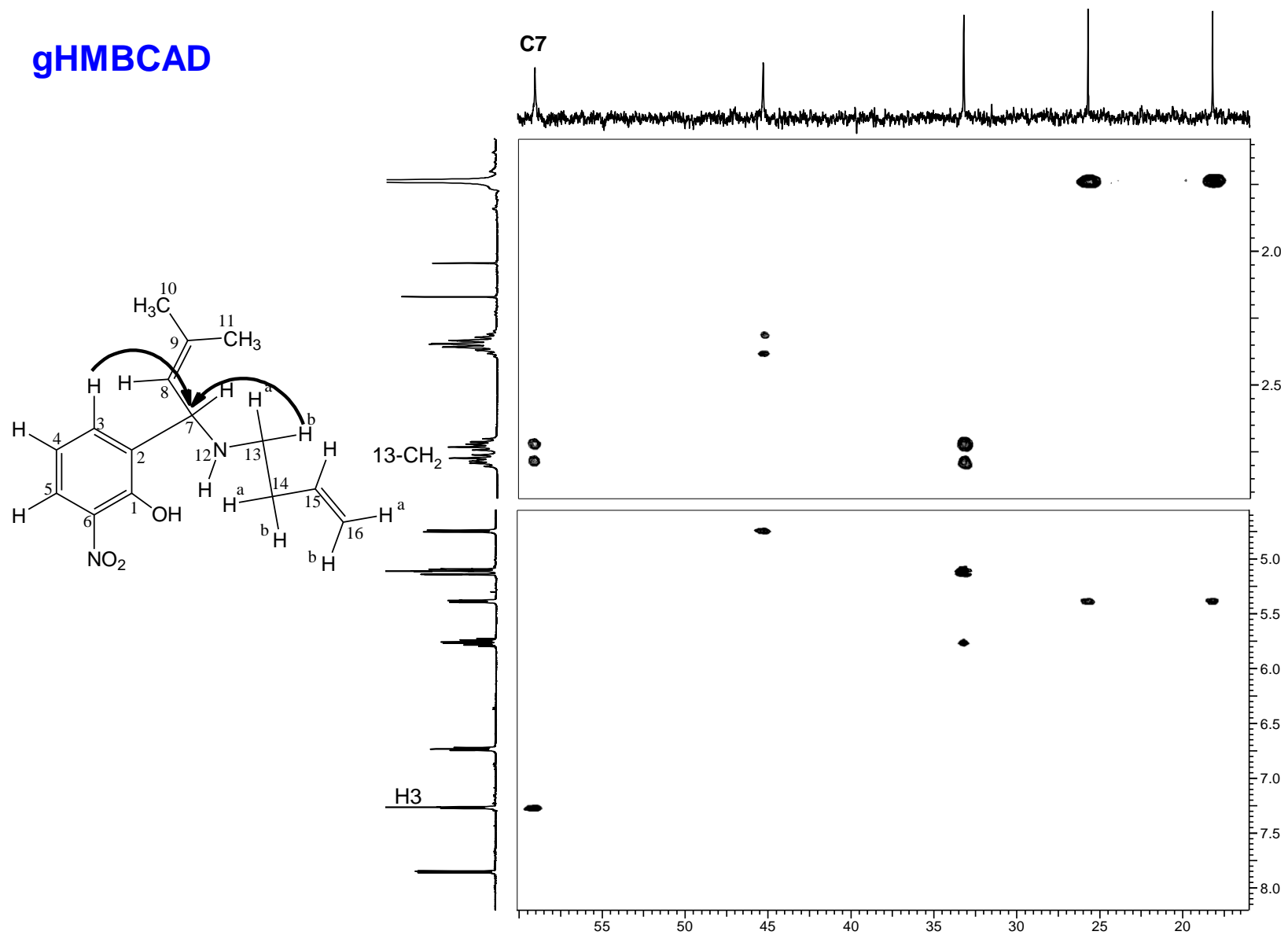


Figure 100: HMBC of Compound **205**